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Intra-Epidermal Carcinoma (Bowen's Disease) of the Vulva

(A Report on Two Cases)

BY

T. N. A. JEFFCOATE, M.D., F.R.C.S., F.R.C.O.G.,
T. B. DAVIE, B.A., M.D., F.R.C.P.,

AND

C. V. HARRISON, M.D., B.S., B.Sc.

From the Departments of Obstetrics and Gynaecology and Pathology, University of Liverpool.

INTRODUCTION.

INTRA-EPIDERMAL cancer of the vulva is said to occur in two forms (Hunt[1]), (*a*) Bowen's disease, (*b*) Paget's disease. As will be shown later there is a good reason to doubt the scientific basis of this classification but, if any differentiation is justified, then the 2 cases described here belong to the former group. Bowen[2] first described this skin lesion on the arm and the buttocks of two men, in 1912, and from histological studies and other considerations concluded that it was a "pre-cancerous dermatosis." Since that time there has been some dispute as to its nature but it is now accepted as being a malignant growth, limited to the epidermis. The microscopic and clinical features of this condition are sufficiently characteristic to have led to its diagnosis on numerous occasions in various parts of the body, including the vulva. In this latter situation, however, it is rare and relatively little known to gynaecologists.

The first case of Bowen's disease of the vulva was described by Hudelo, Oury and Cailliau[3] in France in 1922. Knight[4] in 1943 reviewed the literature and traced reports of 26 cases, to which he added a further 6 treated in the Sloane Hospital for Women, New York, bringing the total for the world's literature up to 32, none of which has appeared in the medical journals of this country. Several of Knight's personal cases are far from typical. In 1, Bowen's disease was discovered microscopically only at the margin of a large fungating carcinoma of 5 years duration. In 3 the history was extremely short and the appearance of the vulva variable, the diagnosis being made entirely on histological grounds, while in another the lesion consisted merely of a small patch of leukoplakia which had produced pruritus for 2 weeks only.

According to Knight,[4] the histological criteria for the diagnosis of Bowen's disease are: (*a*) hyperkeratosis and para-

keratosis, (*b*) acanthosis with marked thickening of the rete Malpighii which appear club shaped, (*c*) loss of stratification of the individual cells with disorientation, (*d*) the presence of nuclear clumping, "corps rondes," nuclear "grains" and mitotic figures, (*e*) an intact basement membrane, (*f*) marked vascularity of the subpapillary zone with round cell infiltration. He points out that it is usually necessary to examine several sections before finding all these features.

Clinical Features.

The naked-eye appearance of the lesion does show some variation, but typically it is a dull red raw area with a clearly defined circinate or serpiginous outline. The area is on the same level as the surrounding skin or at the most is only slightly raised, but there is a sharp line of demarcation between healthy and diseased tissues. The surface is moist but may become encrusted in part, the appearance being very similar to that of Paget's disease of the nipple. It does not show any of the usual characteristics of malignancy: there is no friability or fixation, and metastases in lymphatic glands or elsewhere are rare. It may be confused with eczema, or with tuberculous or other ulcers, and Knight points out that when it occurs on the vulva it may be mistaken for kraurosis (see Case 1) or leukoplakia. Leukoplakia indeed may occur in association with Bowen's disease.

Clinically the disease runs a slow course, often lasting many years. It sometimes heals spontaneously in the central areas, while extending at the periphery. It can at any time, however, change into a frank epithelioma and this is especially true when it encroaches on mucous membranes. At such sites the change into epithelioma with rapid spread and the development of metastases is common.

On the vulva the lesion occurs at any age, before or after the menopause, the ages for recorded cases varying from 25 to 73 years with an average of approximately 50 years. In the second case reported here, however, the patient was 81 years old. The symptoms produced are pain and pruritus, the area often being extremely tender. In long-standing cases a history of remissions and exacerbations is the rule.

Case 1.

C.M., age 67, 2-para. Widow for 25 years.

This patient was first seen on December 12th, 1942, when she was complaining of vulval discomfort consisting sometimes of pain and sometimes of itching, which she had had for 10 months (see later comments on the duration). Tenderness of the vulva prevented her sitting or walking in comfort. There was also slight yellowish discharge of recent origin. The picture was complicated by a small abscess at the base of the right labium minus which had followed an injection of Procto-caine for relief of the pruritus. Menstruation had been regular until 1918 when total hysterectomy was carried out for "malignant disease of the uterus." Further details of this operation cannot be obtained.

When the abscess was healed, vaginal examination was carried out under general anaesthesia and this confirmed that total hysterectomy had been previously performed. She had considerable senile vaginitis, and a bright-red, almost scarlet, raw-looking area affecting the inner and outer aspects of the posterior halves of the labia minora. The introitus had undergone considerable contracture. There was nothing to suggest malignant disease either in the vagina or vulva, and a diagnosis of kraurosis vulvae and senile vaginitis was made, although the appearance was not typical if only because there was a sharp line of demarcation between the healthy and diseased skin. There was no enlargement of the inguinal glands. The W.R. was negative; the urine normal; the fasting blood sugar, 109 mg. per cent, and a test meal showed achlorhydria.

Over a period of months various treatments were given: local antiseptics of many kinds, vitamin A, Acid HCL dil, stilboestrol and several types

of baths. The condition rapidly improved at first, the vaginitis and discharge cleared and the patient was reasonably comfortable. But the raw area on the vulva never healed completely and, after 5 months, it had not only become obvious again but it was beginning to spread on to the right labium majus and the perineum.

The patient was readmitted in May 1943 and it was then quite clear that the condition was not kraurosis vulvae. Treatment by excision of the vulva or the application of radium was contemplated but the patient was averse to excision, and a second opinion was opposed to radium treatment. So further local remedies were tried, sometimes with apparent temporary good results. By July 1943 the lesion was again extending with an edge which had become slightly raised and suspicious of malignancy. Dr. Stopford Taylor, seeing the patient for the first time at this stage suggested the possibility of an intra-epidermal carcinoma, and biopsy was accordingly carried out on July 25th, 1943. On microscopic examination the tissues proved to be heavily infected and it was first suggested that the lesion was an inflammatory one. Careful examination, however, finally revealed one area showing the features of an intra-epidermal carcinoma (Figs. 2, 3, 4).

The patient was anaesthetized again on August 1st, 1943, having agreed to excision of the vulva. However, it was found that the urethral orifice was then involved and total excision was impossible. The condition was progressing rapidly, and by August 10th its edge on the anterior vaginal wall was frankly epitheliomatous and small pieces could be broken off (Fig. 5). Radium was applied in a plaque of dental stent fitting into the vagina and over the affected area of vulva, 12 mg. intravaginal, and 18 mg. covering approximately 20 sq. cm. of vulva. Application was made for 75 hours, the thickness of stent separating the radium needles from the vulva averaging 0.5 cm. (Estimated dose = 6,000 r intra-vaginal and 5,500 r to vulva.) There was considerable local reaction but the vulva gradually healed except for one small area at the base of the right labium minus—the original site of the growth. The patient refused further treatment until she developed a small abscess in the right labium which was incised and drained on April 6th, 1944. At that time she was again examined under anaesthesia and it was found that although the vulva was so much improved, the anterior and right lateral walls of the vagina were extensively involved in epithelioma (Fig. 6). By April 24th, 1944, the abscess had healed but a large fixed mass had appeared in the left side of the neck—almost certainly secondary deposits in lymphatic glands. This was the first sign of lymphatic involvement, the inguinal glands remaining unaffected to the end. A cure was then impossible and radium (40 mg.) was applied by plaque to the vulva, but mainly within vagina, for 35 hours, with the object of relieving the discharge and bleeding. The patient returned home on May 19th, 1944, and at that time the vulva was fairly comfortable, the intense pain and tenderness which had always been a prominent complaint, being much improved. The swelling in the neck continued to increase and her general condition deteriorated rapidly. She later developed signs of respiratory complications and died on July 1st, 1944.

Histology. The predominant feature of sections prepared from the excised portion of skin (Fig. 2) was the dense inflammatory cellular infiltration with plasma cells, lymphocytes and some polymorphonuclears. This reaction, coupled with the superficial erosion of the squamous epithelium very largely obscured the epithelium itself and resembled the picture of non-specific and non-neoplastic ulceration. Close study revealed elongated inter-papillary downgrowths of the epithelium in which hyperkeratosis and parakeratosis were well marked though the typical rounded masses of vacuolated pale staining cells with large blurred nuclei (the *corps rondes*) were few and far between. Mitoses, however, were numerous and all the abnormal features were confined to the epithelium proper (Figs. 3, 4).

The histology of the growth which developed within the vagina is that of a poorly differentiated epithelioma (Fig. 5), but shows also that tendency to vacuolation and enlargement of individual cells which has been referred to as the "Bowenoid" type of carcinoma. Sections taken from the rapidly progressing friable growth at a later stage, after the application of radium, show marked degenerative changes and an almost complete absence of differentiation towards squamous epithelium. (Fig. 6).

CASE 2.•

E.D., age 81, 5-para. Widow for 25 years. Menopause at 53 years.

This patient was first seen on December 10th, 1943, and was referred by Dr. Stopford Taylor who, having seen Case 1 previously, had already made the diagnosis. She complained of: (*a*) pruritus vulvae and sometimes a deep seated throbbing and burning in the vulva for 6 years: there had been remissions but the patient was never entirely free from discomfort, (*b*) occasional bleeding when the pruritus had made her rub or scratch the vulva, (*c*) dysuria, when the vulva was particularly sore. Both labia majora were involved in a lesion presenting a dull-red flat surface with crusts here and there (see colour plate, Fig. 1). The area on the right labium was small but the left labium was extensively involved and oedematous, with the disease spreading on to the inner aspect of the thigh. The edge was typically serpiginous with a sharp line of demarcation. Medially it extended to the vaginal orifice, the labia minora being atrophic. There was no spread within the introitus but the patient had a small urethral caruncle. The inguinal glands were not enlarged. Parts of the right labium not affected by growth showed patches of dark-brown pigmentation. The Wassermann reaction was negative, and the urine normal.

After the experience of Case 1 the diagnosis was easy; the appearance was so characteristic. It was confirmed by biopsy under local anaesthesia, the microscopic appearance being typical (Figs. 7, 8, 9).

Excision of the vulva was considered but the idea was rejected on account of the patient's age and because the wide extension on the left side would have involved removal of a very large area of skin. On December 28th, 1943, 70 mg. radium was applied for 53 hours to the surface of the vulva and the inner aspect of the left thigh by means of a plaque made of dental stent. The area irradiated measured approximately 60 sq. cm., and the distance between the radium needles and the skin averaged 0.5 cm. (Estimated dose = 5,500 r.) There was very little reaction and the patient was discharged from hospital on January 21st, 1944, the vulva being almost healed. Three months later she was fairly comfortable but still had occasional pain and throbbing in the left vulva. The skin of the vulva and thigh was healed except for a few bright red patches on the left labium, which remained slightly oedematous. There was no enlargement of inguinal glands. However, in view of the developments in Case 1, and because of Knight's comments as to the limited value of radium for this condition, the vulva, with an area of skin from the left thigh, was excised on May 15th, 1944. At this time there was no definite naked eye evidence of actual growth but the original area of disease was clearly visible because of the pallor and the fibrous consistence of the skin. The patient made a good recovery from the operation, the vulva healing by first intention.

Histology. (*a*) Biopsy before treatment with radium. The microscopical picture presents the classical features of Bowen's disease as described and depicted in the literature. The superficial layers of the epidermis show hyperkeratosis and parakeratosis and the inter-papillary downgrowths of epithelium are elongated and irregular but retain their limiting membrane. Within the epithelium are numerous *corps rondes*, the structure of which can be seen to be derived from the degenerating oedematous and swollen condition of isolated cancer cells lying among the cells of the stratum malpighii. The nuclei of these cells are greatly enlarged and blurred, with no definite chromatin pattern. Occasionally the cell appears to have collapsed or contracted within its enlarged space and consists only of a small condensed pyknotic clot of nuclear material surrounded by a large rounded clear zone (Figs. 7, 8).

At the growing edge these changes end abruptly (Fig. 9) but they are obviously also within the squamous lining of hair follicles (Fig. 10) and in among the epithelial cells of sweat glands lying in dermis beneath the area of affected squamous epithelium (Fig. 11). In sharp contrast with an ordinary epithelioma it is to be noted that everywhere the basement membrane is intact. There are no free cancer cells in the tissue spaces of the dermis, and the lymph spaces are devoid of cancerous permeation. The degree of reactive inflammatory cellular infiltration beneath the unbroken epidermis is not marked: only where ulceration has occurred, presumably with infection, is the reaction at all prominent.

(*b*) After radiation. Sections from the excised skin show considerable variation in different parts

of the area originally affected. In one area, from the left thigh, healing appears to be complete: the epithelium is intact and there is a complete absence of Bowen's cells. The underlying dermis is only sparsely infiltrated with inflammatory cells, but the epidermis shows atrophic thinning with a well-marked reduction in size of the interpapillary epithelial processes. In sections from 3 other areas of the vulva healing is far from complete or completely absent. Very small areas of the epithelium may be found free from Bowen's cells, but mostly in these sections all the characteristic features of the disease are still obvious. In the section illustrated (Fig. 12) the persistence of the *corps rondes* is obvious not only in the superficial squamous epithelium, but also in the squamous lining layers of one of the hair follicles. In other sections (not illustrated) the Bowen's reaction also persists in some of the sweat glands, though on the whole these appear to have responded more favourably to the irradiation than the squamous epithelium itself.

Comments.

These cases are fully illustrative of all aspects of Bowen's disease of the vulva—its symptomatology, chronicity, clinical signs, histology, tendency to epitheliomatous change, and its response to treatment.

Diagnosis. A late diagnosis in Case 1 undoubtedly resulted in the patient's death; excision of the vulva when the patient was first seen was technically possible and would almost certainly have resulted in a cure. To judge from the literature, delay in diagnosis is not uncommon, and in this case it was 7 months. This was partly because what was probably a spontaneous remission in the disease was regarded as a satisfactory response to the usual treatment for kraurosis vulvae. There were other extenuating circumstances which interfered with the prompt diagnosis and adequate treatment of the case; but the fact remains that if biopsy had been carried out at an early stage the ultimate result might have been different. It should be remembered, however, that even with microscopical sections, the diagnosis was not easy owing to the presence of extensive secondary infection.

The main difficulty in the diagnosis of Bowen's disease would appear to be its rarity and the consequent ignorance of the clinician as to its possible presence. In Case 1, although the lesion had the characteristic macroscopic appearance, four clinicians considered it to be inflammatory in nature even when they had the possibility of a neoplasm in mind. With even limited experience of the disease, however, the diagnosis is not difficult, and in Case 2 it was made at first sight. The importance of biopsy in any doubtful vulval lesion cannot be over-emphasized and this is particularly true when a patient presents any condition which looks eczematous but has a clearly defined edge. With regard to biopsy in these 2 cases, it was especially noted at the time that the tissue was not friable and there was no tendency for the sutures to cut out. Moreover, the incisions in both cases healed rapidly and completely, the sutures being removed by the 5th day; the behaviour was quite unlike that of most malignant tissues.

Etiology. In the literature there are suggestions that arsenic may have been a causal factor in some cases. Thus some patients had received arsenical treatment for syphilis. In these 2 cases, the Wassermann reaction was negative and neither had received arsenic in any form. It has not been possible to trace any connexion between the original "malignant disease of the uterus" and the vulval growth in case 1.

Chronicity. As previously stated Bowen's disease in any site, and the vulva is no exception, may be present for many years without threatening life or seriously in-

conveniencing the patient. In case 2, the lesion had been present for at least 6 years. In Case 1, the patient originally stated the duration of symptoms to be 10 months. However, prior to her leaving hospital on the last occasion, and after she had given some considerable thought to the events of her medical history, she volunteered the statement that one year after hysterectomy she went back to see the surgeon on account of irritation of the vulva, limited she said to one red spot on the right side. She was reassured and did not receive any special treatment, but from then onwards she had intermittent discomfort in the vulva, always having to be careful not to sit down heavily.

She found it more comfortable to sit on the left buttock first. This history is a little suggestive that she may have had the lesion for 24 years, with exacerbations and remissions. This suggestion is not unreasonable although the longest period recorded in the literature of Bowen's disease of the vulva is 11 years. However, cases of Bowen's disease elsewhere in the body have been recorded with a history extending over a period of 29 years.

Epitheliomatous Change. An intra-epidermal carcinoma may at any time develop into frank epithelioma. There are at least 2 reported examples of this occurrence in the literature of vulval cases. In Case 1 the vulva was not involved in epithelioma but the vagina reacted like a mucous membrane, for as soon as the lesion reached it the change into epithelioma occurred within 1 or 2 weeks. Its subsequent behaviour and change in type is also worthy of comment. It was only temporarily checked by the initial application of radium and afterwards its spread was rapid and it quickly metastasized in cervical lymph glands, and possibly within the thorax. By that time its histological appearance had changed and it consisted of dedifferentiated cells of a highly malignant character. (Fig. 6).

There are two possible factors which determined the development of epithelioma in this case. The patient initially received oestrogen therapy and over the course of the first 6 months she was given, intermittently, approximately 250 mg. stilboestrol. The effect of this cannot have been other than harmful, since it must have proved a powerful stimulus to the epithelial cells of the vulva.

The initial radium treatment may also have played a part in the rapid extension in the later stages. Knight found in the literature several references to the poor results of radiotherapy, and suggestions that in some cases it appeared to lead to a more rapid extension of the lesion. In Case 1, however, epitheliomatous change had certainly occurred before radium was applied. It is impossible to state whether, in the dosage employed, it determined a change to a more malignant type of growth.

Treatment. Although Hunt advises radium for intra-epidermal carcinoma of the vulva, the opinion of those who have used radiotherapy for Bowen's type of growth is that the results are not always satisfactory. Recurrences, or even a rapid spread of the growth may follow its application. The better treatment is by local excision of the vulva, or of the area involved, and the results so far reported are good, although some patients have had recurrences necessitating further excision. Excision of the inguinal glands is unnecessary. The effect of radium in Case 1 is difficult to assess because of the associated epithelioma. Nevertheless, the first application did not eradicate the vulval condition completely. The dose may have been too small and the second application appeared to have a better effect on the

vulva—at least for the short period during which the patient was observed afterwards, but histological evidence of this is not available. In Case 2, the lesion rapidly improved following radio-therapy. Nevertheless, the naked eye and symptomatic effect proved deceptive and sections taken 5 months later show the presence of intra-epidermal cancer, in 3 out of 4 areas. The patient would certainly have had a recurrence of symptoms had excision been delayed further. Personal experience therefore goes to confirm the view that patients suffering from this disease should whenever possible be treated by excision of the affected area. Not only is the ultimate result likely to be better but the patient is spared the extreme discomfort of the reaction which so often follows the application of radium to the vulva. If excision is impossible, however, radium does offer the prospect of temporary relief, if not a permanent cure. The final result in the second case remains to be seen, but the prospects for a cure are reasonably good.

Pathology. Consideration of the pathological aspects of Bowen's disease would not be complete without reference to Paget's disease of the vulva, a condition which, as mentioned previously, has been reported as a separate type of intra-epidermal carcinoma. Judging by published reports, this too is a rare lesion of the vulva, but isolated cases have been described from time to time. Hunt, in her book, mentions and illustrates one, and the latest report is by Traub.[5] During the discussion on this latter case Cooper commented that it was only the fifth or sixth recorded in the literature; this, however, is probably an under-statement.

Paget,[6] in 1874, described an eczematous condition of the nipple which is associated with an already apparent carcinoma of the breast or with the subsequent development of such a cancer within the breast. In a series of studies Muir[7, 8, 9] established, to the complete satisfaction of the great majority of pathologists, that the lesion of the nipple and areola in these cases is due to the penetration of the squamous epithelium by cells of an "intra-duct" carcinoma of the breast. This "intra-duct" carcinoma develops in chronic mastitis and consists of a proliferation of the lining cells of a lactiferous duct. The lesion is at first confined to the lumen of the duct; there is no rupture of the ductal basement membrane but the cells grow up and down the duct. The cells at the site of origin of the lesion, or from above or below this situation, may at any stage invade the wall of the duct, and break through into the surrounding tissues. Only when this happens does the lesion present the usual clinical and microscopical features of mammary carcinoma. Cells which ascend the duct and reach the nipple may pass out and penetrate the squamous epithelium in which they set up the eczematous condition known as "Paget's disease." In sections of the epithelium these cells appear bloated and pale and sometimes show bizarre nuclear formations. They constitute the most striking histological features of the condition.

Paget's disease of the nipple is thus an intra-epidermal carcinoma in which the neoplastic cells are of non-squamous origin (being, in fact, derived from the lining epithelium of the lactiferous ducts), and in our opinion the term "Paget's disease" should be strictly confined to this lesion of the breast. The indiscriminate application of the designation to eczematous or other lesions of the skin in other parts of the body fails to take regard of the pathology of the lesion which develops on and around the nipple, and inevitably leads to confusion with other cancerous or precancerous lesions of the skin. On a pathological and etiological basis it is manifestly difficult to

justify the use of the term "Paget's disease of the vulva," though admittedly it is conceivable that a cancerous process arising in the lining epithelium of the ducts of Bartholin's gland might reach the vulval skin and produce a lesion around the orifices of those glands analogous to Paget's disease of the nipple. Of the recorded cases of Paget's disease of the vulva it is doubtful whether any would justify their designation on these grounds.

Intra-epidermal cancer, however, is apparently not limited to epithelial invasion by cells from non-squamous carcinoma. In Bowen's disease of the skin the epithelium over a large and gradually extending area is invaded by cancer cells which have apparently originated within the squamous epithelium. In this condition, however, the cancer cells, unlike those of the epithelioma or of the rodent ulcer, do not at once invade the sub-epithelial tissues of the skin but remain confined within the epithelial layers—at any rate for some time. In this respect it resembles Paget's disease of the nipple. There is also a resemblance in the type of cell present. In both Paget's disease of the nipple, and Bowen's disease of the skin, the epidermis is infiltrated by large vacuolated cells with bizarre nuclei. Although these cells arise from different tissues, the similarity of the picture which they produce has given rise to confusion and has led to the description of Paget's disease on the vulva and at other extra-mammary sites; sites at which, if the present concept of its pathology is true, it cannot occur.

The two conditions have been more readily confused because the naked eye appearances of the lesions are similar and they both run a chronic course, frank cancer making a relatively late appearance. The description and illustrations of Paget's disease of the vulva are identical with those of Bowen's disease (cf. Knight and Hunt). We suggest, therefore, that the cases recorded as Paget's disease of the vulva have in fact been cases of Bowen's disease. The only possible exception to this conclusion is when the cancer cells have arisen in Bartholin's duct and have invaded the skin. Even so, it is doubtful whether such a hypothetical lesion should be termed Paget's disease, which, by virtue of tradition and its pathogenesis, should be reserved only for the condition as it appears on the nipple. Indeed, so far as the vulva is concerned there is much to be said for abandoning the use of such terms as "Bowen's disease," and for employing the more descriptive intra-epidermal carcinoma.

The factor which determines the confinement of the cancerous process within the layers of the squamous epithelium of the affected area is as yet a complete mystery. The restriction on the spread of cancer cells which is imposed by basement or other limiting membranes of epithelia is well recognized, but in the great majority of cancers the powers of such barriers are short lived. Once the break through has occurred, the spread of cancer cells along lymphatics and intercellular tissue spaces rapidly produces the well-recognized pathological and clinical features of a cancer. It is arguable that every squamous-cell carcinoma of the skin actually commences as an intra-epidermal cancer, but only those in which the intra-epidermal phase persists for some time are entitled to the designation of Bowen's disease. That the intra-epidermal feature is only a phase of uncertain and variable (though relatively prolonged) duration is shown by the histories of numerous cases of Bowen's disease of the skin of the vulva and of other parts of the body. It is the ever-present risk of this change in all cases which justifies our advocating complete excision as soon as it is diagnosed.

FIG. 1.

Case 2. Intra-epidermal carcinoma of the vulva.

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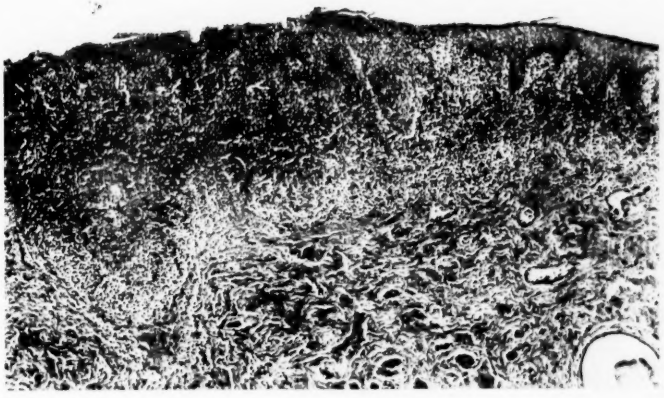

FIG. 2.

Case 1. Section showing edge of ulcerated area. The heavy infiltration of inflammatory cells obscures the lesion in the epithelium but the absence of any epitheliomatous downgrowths is well shown. (× 28)

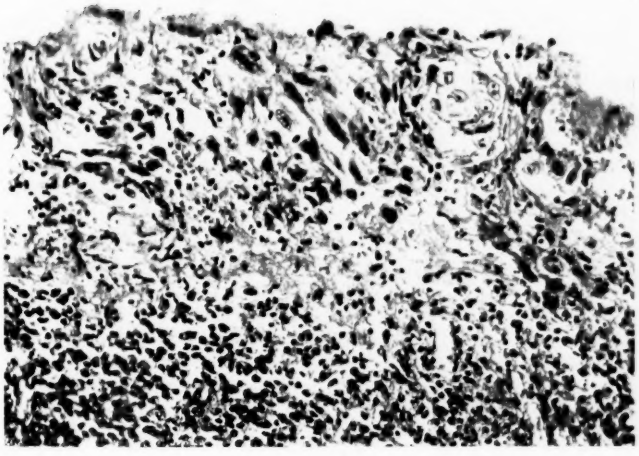

FIG. 3.

Case 1. Portion of the epithelium over the affected area showing abnormally swollen cells, some with malignant hyperchromatic nuclei. (× 240)

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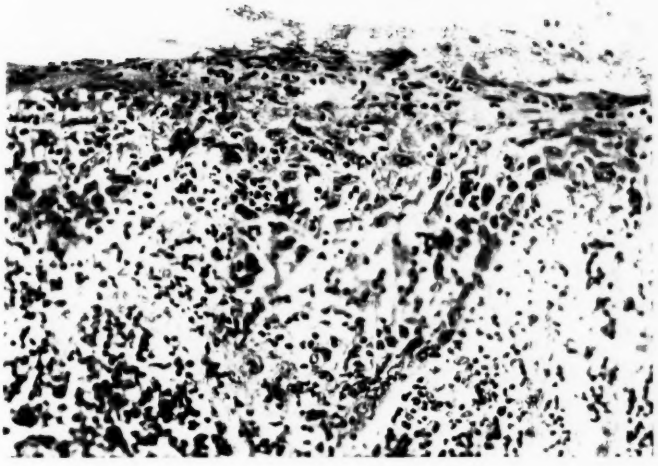

FIG. 4.

Case 1. Another portion of the affected epithelium showing inflammatory cellular infiltrations. A bloated Bowen's cell is visible at the lower left side of this inter-papillary process. (× 240)

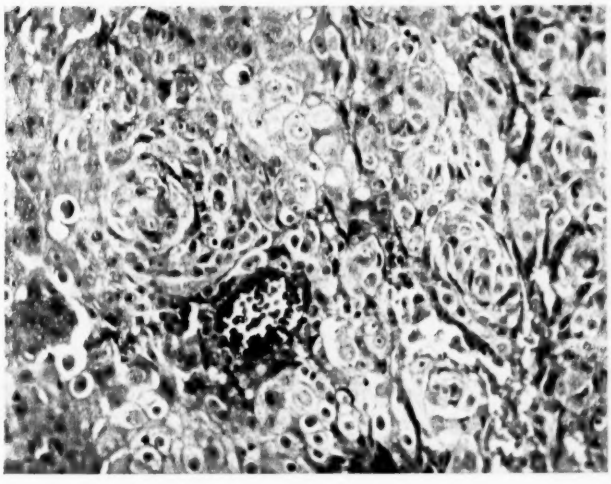

FIG. 5.

Case 1. "Bowenoid" type of epithelioma which developed within the vagina shortly after the skin lesion had spread to the wall of the vagina. (× 120)

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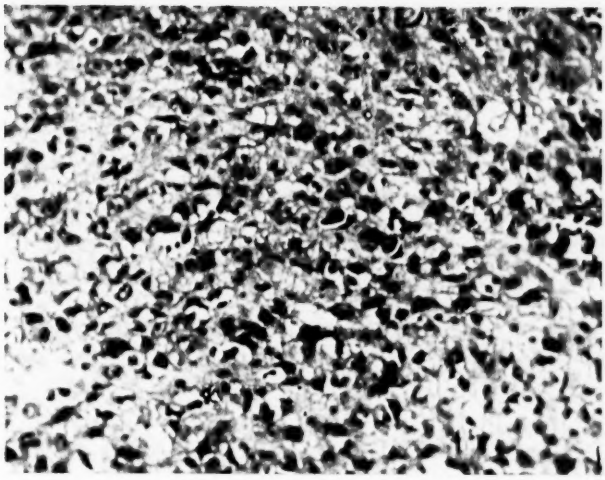

FIG. 6.

Case 1. Degenerating anaplastic type of carcinoma found in the vagina after treatment with radium. An occasional "Bowenoid" cell can still be seen. (× 240)

FIG. 7.

Case 2. Low power view of lesion showing hyperkeratosis and the elongation of the inter-papillary epithelial processes. (× 40)

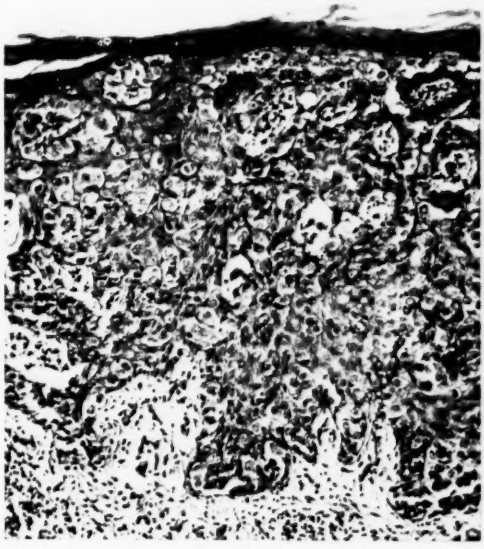

FIG. 8.

Case 2. Higher power view of affected epithelium showing the "corps rondes" and the restriction of the cancerous process within the basement membrane of the epithelium. (× 110)

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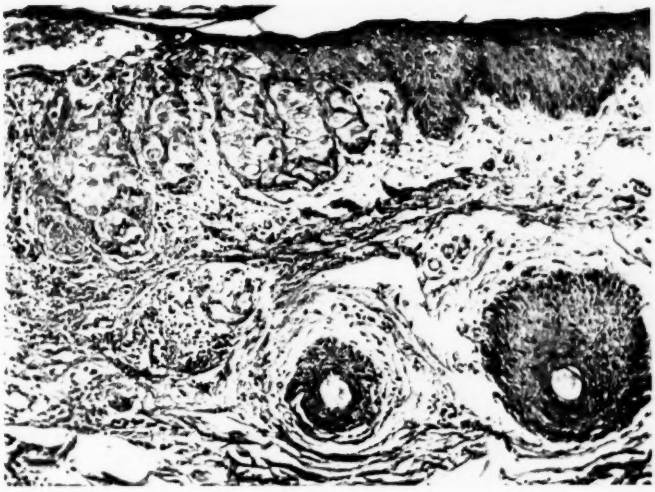

FIG. 9.
Case 2. The growing edge of the lesion to show the sharp demarcation between healthy and affected epithelium. (× 100)

FIG. 10.
Case 2. Hair follicle affected by Bowen's disease showing bloated Bowen's cells within the squamous epithelium. (× 240)

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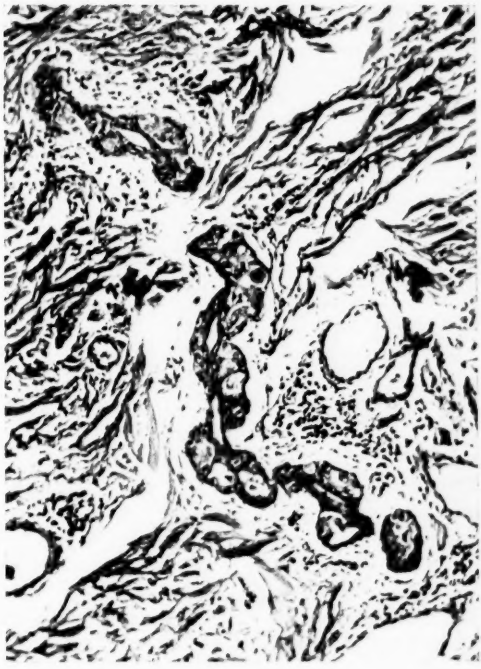

FIG. 11.
Case 2. Sweat gland affected by Bowen's disease.
(× 240)

FIG. 12.
Case 2. Low power view of affected skin after radium treatment, showing absence of beneficial result. Bowen's cells are obvious throughout the epithelium and are particularly well marked in the lining of the larger hair follicle. (× 20)

UNIV. OF MICH.

SUMMARY.

1. Two cases of intra-epidermal carcinoma (Bowen's disease) of the vulva, are described in detail.

2. In the first patient the lesion ultimately spread to the vagina and immediately changed into epithelioma which rapidly assumed the most malignant characters.

3. The clinical features of this condition are described and the diagnosis, etiology and treatment discussed.

4. Special reference is made to its pathology and its relation to "Paget's disease of the vulva." It is suggested that cases previously described as Paget's disease have in fact been cases of Bowen's disease and a plea is made for a restriction of the use of the former to the well-known lesion of the nipple.

5. The results of treatment in these 2 cases go to substantiate other reports that the use of radium is not satisfactory and that excision of the affected area is preferable. In neither of these cases was the growth process arrested by radium application.

In conclusive we wish to acknowledge with gratitude the help and advice in the diagnosis and management of these cases given by Dr. R. Stopford Taylor and Dr. M. A. Stewart (Radiotherapist). The colour plate is prepared from a film taken by Mr. C. M. Marshall without whose kindly help it would have been impossible to obtain any permanent record in colour.

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The Control of Staphylococcus Aureus Infections in a Maternity Department

BY

F. A. KNOTT, M.D., F.R.C.P., D.P.H.

Director, Bacteriological Department, Guy's Hospital,

AND

J. B. BLAIKLEY, F.R.C.S., F.R.C.O.G.

Assistant Obstetric Surgeon, Guy's Hospital; Surgeon to Out-patients, Chelsea Hospital for Women.

DURING recent years there has been an increase of staphylococcal infections in maternity wards; for this a variety of reasons might be suggested; dietetic deficiencies, black-out conditions and poor ventilation, cutaneous irritation by inferior soaps and powders, or increased prevalence of invasive staphylococci are all possibilities. But, whatever the primary causative factor, an essential point in prevention must be the systematic exclusion of the organisms; also, as absolute perfection in this respect is probably unattainable, some reasonably workable routine is required to avoid the spread of any invasive staphylococci which do gain access to the ward.

To obtain direct evidence as to how nearly, using quite simple methods, both these objectives could be achieved, bacteriological examinations of the patients, personnel and premises of the Guy's Hospital Maternity Department were begun in the first weeks of 1942 and have now been continued for approximately 2 years and 3 months, during which time there have been 600 confinements. The Department as a whole is entirely self-contained, having its own theatres and preparation room, a specially equipped nursery, a kitchen and dairy and the usual accessory rooms. The main ward accommodates 24 women in well separated beds. Separate observation and isolation annexes are available. The medical, nursing and domestic staff total 29. A few of these are relatively permanent, but the majority such as the dressers and probationer nurses change at intervals.

At the time this work was begun the Department was experiencing a series of sharp outbreaks of staphylococcal sepsis, starting suddenly and subsiding gradually within 2 or 3 weeks. Each group of infections included the usual variety of lesions, namely mastitis, breast abscess, genital infection with mild puerperal pyrexia, and occasional wound sepsis among the mothers; conjunctivitis, septic cutaneous spots, nasal discharge, and often true pemphigus among the babies. Particular attention was paid to the last because the bacteriology can, by aseptic puncture of unbroken bullae, be determined with some accuracy. On four occasions this type of infection was predominant, and the staphylococci appeared to breed true; good opportunity was thus provided of confirming lines of spread.

To begin with, our main object, apart from detecting and removing infected individuals, was gradually to map out, both at

the time of and between the outbreaks, the distribution of *Staphylococcus aureus* in the Department. It soon became obvious, as explained later, that human carriers played a major part in re-introduction of infection and that after introduction direct contact, especially by hands, was very important in the subsequent spread. But as outbreaks continued to develop it was clear that our preventive measures were at that time either incomplete or too slow in operation and an attempt was therefore made to formulate a much more strict routine. The scheme described later was officially introduced on March 1st, 1943, and has been adhered to strictly ever since. No other changes were made in the Department, the general conduct of which had been as much in accord with the recommendations of M.R.C. Memorandum No. 6 on "The Prevention of Hospital Infection of Wounds," 1942, as wartime conditions allowed. The diet, black-out, ventilation, kitchen and laundry routines and the source and number of the staff all remained the same. Under the old conditions, March 1942 to February 1943, there were 225 confinements; under the new, March 1943 to February 1944, 375 confinements. Comparison between the sepsis records of the two periods indicates, as shown in subsequent sections of this note, the measure of control obtainable by the quite simple new measures adopted. As these conform in a number of respects to the further and more recently enunciated principles of M.R.C. Memorandum No. 11 on the "Control of Cross Infection in Hospitals," 1944, the good results obtained have special interest at the present time.

Specimen Collection.

While investigating the outbreaks of the first year and operating the control in the second, approximately 8,000 bacteriological specimens were examined. These came from the patients' lesions and from the skin, hands, respiratory tracts and other likely sources of infection in both patients and staff and from the dust and every kind of equipment in the ward. No new technical methods were employed but particular care was taken to avoid contamination and to inoculate and incubate all cultures immediately after collection.

Whenever possible very fresh lesions were chosen for examination. Many were sampled by aseptic puncture. In those already discharging, all surface material was carefully wiped away before final culture was made from fresh, deep exudate. Cultures from the nose, pharynx, eyes, vagina and catheter urines were made in the usual way. Hand and other cutaneous cultures were obtained by firm rubbing of the surfaces with either sterile swabs or small gauze squares previously moistened in sterile normal saline. With both swab and square, after 5 hours incubation in broth, surface plating on to fresh blood agar followed. In taking all forms of skin culture the swab or gauze was passed well into the folds, between the fingers and round the nail edges according to the site examined. Dust samples from the surfaces of floors, utensils, etc., were taken by firm contact with sterile lint squares moistened with saline and held in forceps and subsequently thrust into broth tubes. After 5 hours incubation, these, as in the case of hand cultures, were plated on blood agar. On many occasions blood agar plates were also exposed to the air of the wards for periods of 5 to 10 minutes. The initial growth from practically all the fresh or unbroken lesions examined gave pure growth of apparently a single strain of *Staphylococcus aureus* but whether cultures were pure or not, the subcultural reactions of 2 or 3 separate colonies were always observed before the organism was

classified as described in the next paragraph. In possible carriers the number of colonies present in a direct plating as well as the Grade were, in deciding questions of exclusion, etc., taken into consideration. A very few isolated colonies of a Grade A strain would condemn. Considerably more were required with less invasive varieties.

Characters of Infecting Staphylococci.

As all past experience has shown that attempts to assess the pathogenicity of different strains of *Staphylococcus aureus* upon the basis of any one cultural character have to some extent failed, it was decided to test each strain generally. The infecting organisms were then, using the usual standard methods noted below, graded according to biochemical activity as a whole.

For assessment of pigment and haemolysin production immediate platings on 5 per cent rabbit blood agar were first incubated overnight at 37°C. and then stood in a North light at 18°C. for the next day. Coagulase formation was noted by adding 0.1 c.c. of an overnight broth culture to 0.5 c.c. of fresh human plasma diluted 1 in 10 with normal saline, the tubes being placed in the 37°C. incubator for 3 hours and then allowed to stand at room temperature overnight. Coagulation during the first 5 hours was taken to indicate an actively positive strain and recorded as 'three plus.' Weaker grades coagulated only after longer standing. Known positive and negative controls were run at the same time with the same plasma. The fermentation tubes, initially of *p*H 7.6 to 7.8 with phenol red as indicator and containing 1 per cent of each carbohydrate, were inoculated with one drop of a saline emulsion of the staphylococcus made up to a standard opacity of approximately 2,000 million per c.c. and incubated at 37°C. over 3 or 4 nights if necessary before a final reading was taken. The gelatin stab was incubated for 3 nights at 22°C. By recording not only the positiveness of the reactions but also, as small appended numerals, the approximate time in hours before the result was evident, the more active strains could be quickly noted and ultimately the particularly inactive also. A working classification is shown in Table I.

Table I.

		Pigment	Coagulase	Haemolysin	Gelatin	Mannite	Lactose	Sacchar.	Maltose	Glucose	
Grade	A	+ + +	+ +	+ + +	+	A_{24}	A_{24}	A_{24}	A_{24}	A_{24}	A
,,	B	+ + +	+ +	+	±	A_{48}	A_{24}	A_{24}	A_{48}	A_{24}	B
,,	C	+ +	±	±	∓	A_{72}	A_{48}	A_{48}	A_{48}	A_{24}	C
,,	D	+	∓	∓	−	A_{72} or —	A_{72}	A_{72}	A_{48} or 72	A_{24} or 48	D

All Grade A and B strains are considered invasive and exclusion of the patient or carrier follows.

With an arbitrary grading of this nature it is not to be expected that every strain will fall unquestionably into a particular grade, but in practice we found not more than 10 per cent of 'doubtfuls' and for preventive purposes these were given the benefit of the doubt and upgraded to rank as Grade B, and therefore, in accordance with our clinical findings, as possibly invasive.

Staphylococci Present in Different Lesions.

If one summarizes as in Table II the grading of the staphylococci found in the various types of staphylococcal lesions we met with in staff, mothers and babies, it is seen that the more severe Grades A and B predominate markedly. It is unsafe to generalize from the findings in a small number of cases but all our experience during over 2 years goes to show that frankly Grade A and B strains tend to result in the clinically more severe infections.

Table II.

Lesions	Staphylococcal Grades A	B	C	D
Breast (Abscess)	3	3	0	0
Breast (Inflamed only)	3	9	5	1
Pemphigus	15	14	2	0
Impetigo	1	2	1	0
Septic rash or boils	9	24	7	3
Septic finger	5	3	1	0
Conjunctivitis	2	16	6	1
Wound sepsis	2	4	0	0
Fifty consecutive "Normal" but + skins in mothers	1	4	17	28

It will be noted later that in three of the outbreaks the staphylococci were 'typed.' This was done according to the Cowan[1] technique. Pressure of work prevented Dr. Gillespie from testing our strains himself so he very kindly provided us with standard subcultures of his Types I, II and III, together with full technical details. After two rabbit passages we obtained good rabbit-agglutinating serum from each. Very clear-cut slide agglutination readings were obtained with main types I and III. With type II results were not unequivocal and, probably owing to lack of experience with the method, we were unable really satisfactorily to differentiate between subtypes a, b, c, etc. However it will be seen that at least some evidence useful for our present purpose was obtained, since in these outbreaks the strains met with in those infections connected by circumstantial evidence all reacted clearly as being of the same main type. For the really rapid detection of carriers and their exclusion before infection is spread the method seemed too time-consuming, and our experience has been that simple 'grading' is a more practical proposition in relation to a busy maternity department. Accurate typing is, of course, of the utmost value in confirming obscure lines of spread or proving unexpected sources of infection, but as a first measure, it seems likely always to be at a disadvantage owing to the extra time required. The same may possibly be the case with the more recently introduced phage typing of staphylococci which in our experience has taken decidedly longer than preliminary grading. On this point judgment should, we think, be reserved until standard phages become generally available, because the method is undoubtedly promising. The clinical facts on which this note is based prove, however, that speed is of the utmost importance and that outbreaks can be quickly stopped only if the bacteriological methods are correspondingly rapid.

Continuous Graphic Record.

In order to give immediate easy reference to the bacteriological position in the Department from day to day over long periods a

continuous graphic record was kept in the laboratory. It is obviously impossible to reproduce more than a short section of this but the principle may be illustrated by taking the record, as shown in Table III, of the development of Outbreak III in mid-1942.

Large sheets of squared paper are pasted to three-ply wood and hung on the laboratory wall. Above are kept the records of the staff and, immediately below them, the findings for the mothers and their babies; so that a vertical line through the whole record at once gives the position at any particular time. Lower still are entries concerning any tests made of ward dust, equipment or visitors. In practice entries are made with coloured pencil, a horizontal *green* line showing freedom from *Staphylococcus aureus*, a line in *black* with letters appended indicating the presence of *Staphylococcus aureus* grade C or D and a similar entry but in *red* recording the presence of Grades A and B. A small black vertical entry marks the exclusion of the individual from the ward and the exact date.

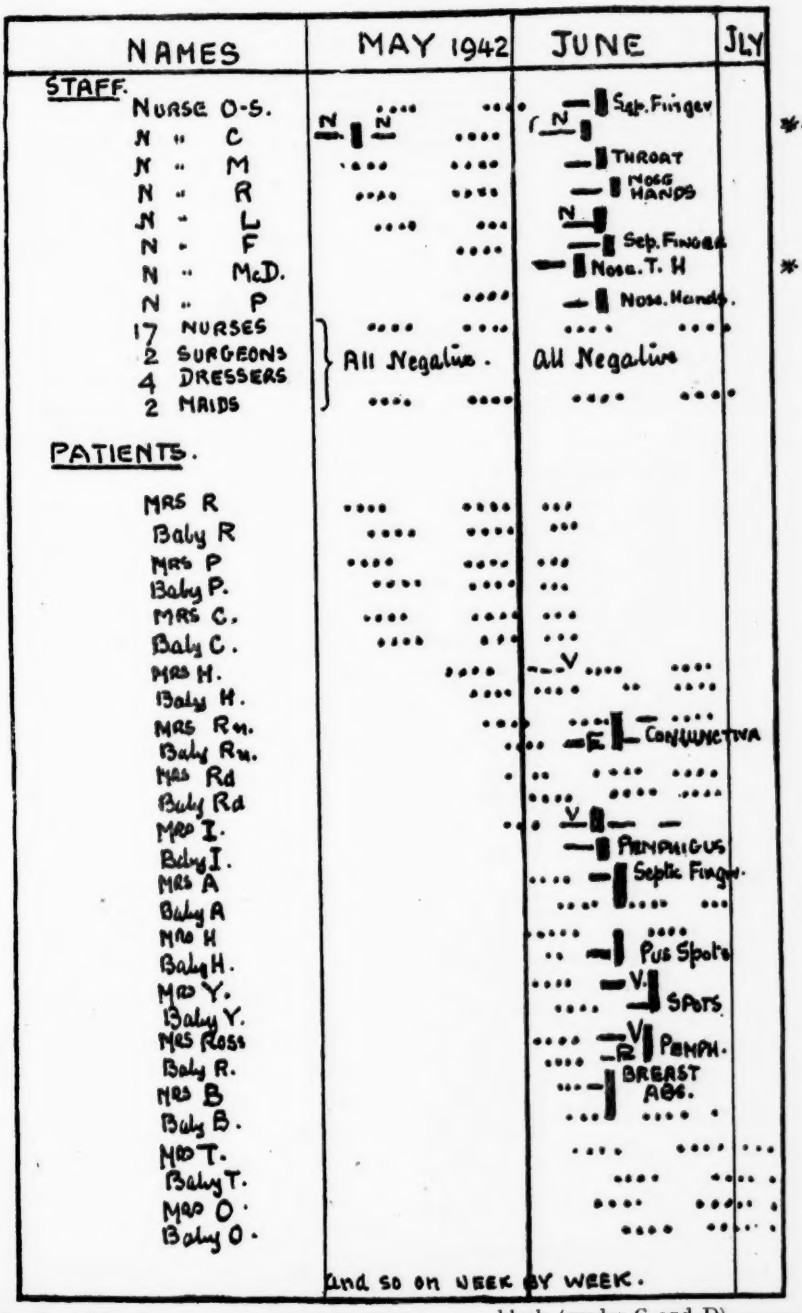
A glance at the chart then immediately shows the course of the outbreak and assists in quick decision as to what exclusion and isolation measures should be taken. In Table III the entry of the nurse carrier, Nurse McD., allowed on duty without previous swabbing is shown at.* It was unlikely that the nurse marked** caused this outbreak as, although she gave positive nasal cultures a month previously, and went off duty, she first became free and then in June was found to be infected by a different strain, the same one in fact as brought in by Nurse McD., and she had evidently been re-infected from her.

Sources of Infecting Staphylococci.

Staphylococci can reach the department from carriers (respiratory tract, hands, etc.) among the patients and staff, in dust or materials introduced from other parts of the hospital, and with visitors. During the first year the outbreaks were considered chiefly from this point of view. Although by exclusions and cleaning each outbreak could gradually be brought to an end, and meanwhile evidence obtained as to the source of infection, at first, and until the ward staff had been convinced of the necessity, it was difficult to maintain a continuous prophylactic routine. Thus the first year shows five infected periods. After the first four came spells of freedom until, through lack of proper precaution, someone, ultimately proved a carrier, apparently again introduced infection. After the fifth had been cleared early in 1943 the bacteriological evidence was put before the administrative staff concerned and held to justify strict enforcement of the routine described later. The year 1942 covers therefore a period of observation and limitation of outbreaks, prophylaxis being meanwhile imperfect, and 1943 and early 1944 a period under really strict prophylactic routine.

Outbreak I. Considering the 1942 outbreaks in turn, the first, which was in progress when these observations began (Jan. 1942), comprised 9 cases of pemphigus, 3 of septic rashes, 4 inflamed breasts, 1 with abscess, and 2 cases of conjunctivitis; and over the same period 7 nurses and 2 dressers were found to be carrying Grade A *Staphylococcus aureus* in nose, throat or hand cultures. At the time similar positive cultures were obtained from some dusting powder, a bottle of olive oil, two towels used on babies and a large roller towel in the kitchen. As might be expected several positive cultures were also given by the bed clothes of infected patients. In spite of this wide distribution among personnel, the actual ward dust was singularly free from *Staphylococcus aureus*

TABLE III.



In the table above ..... represents green, ----- black (grades C and D) ——— red (grades A and B). A vertical entry | indicates exclusion and, according to position, may be seen to occur before or after actual entry to the main ward. The records of those never allowed into the main department are ringed thus: (———— —)

which grew only three times among 30 samples, and of these one from under an infected baby's cot, was the only Grade A strain. As to the origin of this particular outbreak some doubt must exist because it was well started before systematic cultural work began. But two points are noteworthy. Taking the records as a whole the very active Grade A strains are not particularly common, especially among carriers. When cultures were first taken, all the infected mothers and babies except one gave Grade A organisms apparently identical in culture and subsequently shown to belong to Cowan's type III. From the hands of seven attendant nurses apparently the same staphylococcus was grown. It was obtained also from a damp roller towel in the kitchen and it is probable that this towel was the real cause of the initial introduction. About a week before the outbreak began, air-raid repairs had necessitated the temporary housing of a few surgical cases in a semi-closed adjoining ward. One, a small girl previously operated upon for mastoiditis, was subsequently shown to be heavily infected by a Grade A, type III *Staphylococcus aureus* and, as no other pathogens occurred in her wound, this staphylococcus was presumably present when she was admitted. In the next bed an appendix case developed wound sepsis due to the same variety of staphylococcus and then, three days later, the first infections appeared in the neighbouring Maternity Department. Enquiries showed that owing to difficulties in the above temporary arrangements two nurses looking after the surgical cases had, in spite of the rules, made occasional use of the maternity ward kitchen and its towel.

Outbreak II. The above series of infections had been sufficiently severe to necessitate, as soon as all patients could be isolated or were sufficiently improved to send home, closure of the Department, which was then thoroughly cleaned and restocked with clean linen, new equipment and freshly sterilized materials. Unfortunately, when it opened again 10 days later, the majority of its former staff were again on duty. For this there were two reasons. The bacteriological tests had not strictly included everyone, and it is doubtful whether those in administrative control had at that time realized the urgent necessity that they should. Twenty random dust samples taken in different parts of the Department were all found to be free from Grade A or B *Staphylococcus aureus*. In any case within 5 days staphylococcal sepsis among the patients had broken out again. The surgical cases in the adjoining ward had been removed long ago. Therefore the human carrier within the Department seemed to be the most likely explanation and a complete bacteriological examination of everyone was at once undertaken. Briefly it may be said that 5 of the previously infected nurses were found still to be carrying the Grade A, type III staphylococcus on their hands or in their respiratory tracts. They passed it on to 2 others and among the patients there were 7 cases of pemphigus, 4 of purulent skin sepsis, 5 of conjunctivitis, 3 inflamed breasts and 1 vaginal infection with pyrexia.

Interval. After this experience it was decided again to close and clean the department, later dust cultures having shown the presence of the staphylococci. Complete spring-cleaning was undertaken and the maternity work meanwhile moved to the floor of the private block formerly devoted to midwifery but closed during the war. After it had been prepared, care was taken first to prove that no Grade A or B staphylococci could be found in direct cultures from the floors, walls, cupboards, etc., of the new premises. Also every member of

the staff was very carefully re-examined and hand, skin and respiratory tract cultures were taken, and 5 were excluded and replaced by others shown to be free of *Staphylococcus aureus*. It was decided to take also skin, respiratory tract and vaginal cultures from all new admissions and to 'barrier nurse' any showing staphylococcal infection by Grade A or B strains.

For a month the Department carried on in its new quarters without sepsis of any kind. It then moved back to its original home with the same staff, and still no infections appeared during the next few weeks.

Outbreak III. This freedom from trouble undoubtedly resulted in some relaxation of precautions and early in June a nurse was allowed to join the Department, and, unknown to the bacteriologists, to go on duty without preliminary cultures being taken. She was suffering from severe hay fever and recurrent colds, being an allergic of long standing and a well-known visitor to the Inoculation Clinics, and heavy growths of a Grade B *Staphylococcus aureus* were repeatedly obtained from her nasal cultures. Among her patients a mother developed an abscess, Grade B, type I, and, although her infant showed no lesions, those from the beds on either side both developed several mild pemphigus bullae from which the same staphylococcus was grown. As seen in Table III, which records this particular period, infection spread to at least 6 nurses previously free, producing septic fingers in 2 of them, and among the patients there occurred, apart from those mentioned above, 2 septic rashes and 1 marked conjunctivitis in the babies, and 1 septic finger, 1 inflamed breast, and 2 vaginal infections in mothers. All except the last 2 proved to belong to Grade B, type I. Possibly because the bacteriological work had now been systematized and the results made more quickly available, immediate exclusion or isolation of those infected seemed to bring the outbreak to a close. New admissions were stopped for only 3 days. Some extra cleaning, re-sterilization and re-stocking was carried out but the department was never closed and within a fortnight of the appearance of the first case, the breast abscess, the whole unit was, according to widespread bacteriological tests, again free from Grade A and B staphylococci.

Interval. The events of Outbreak III revived administrative interest in systematic swabbing and for the next 10 weeks relative freedom from Grade A and B strains were maintained. To achieve this 4 nurses and 1 dresser were sent off duty (4 colds and 1 mildly inflamed finger, all Grade B) and 10 new admissions had to be isolated or put on "precautions" (1 nasal Grade A, 2 nasal Grade B, 4 tonsil Grade B, and 4 vaginal Grade B, 2 of the latter showing mild pyrexia). The only apparently new infections arising among the patients during this period were: 1 infected Caesarean section wound, 1 mildly inflamed breast in mothers, 3 mild instances of conjunctivitis, and 6 mild septic rashes in otherwise normal babies. All were due to Grade B strains.

It is important to note also that throughout this time, and in fact throughout the whole of the 2 years review, no attempt has been made to exclude Grade C and D strains except on the very rare occasions when they were found to be producing significant lesions.

Outbreak IV. As before, this spell of freedom resulted in some slackening of precautions. In October a patient was admitted in the late stages of a severe head cold. Unfortunately she missed being

swabbed. Subsequently it was found that she had a marked secondary antral infection with a *Staphylococcus aureus* Grade A, type III. Up and about the ward for several days before confinement, attention was only called to her by severe pemphigus developing in 2 babies from beds adjoining hers. Born 4 days later, her own baby showed similar lesions. Four nurses, previously proved free, showed the organisms on their hands and 1 developed an infected finger. One neighbouring mother, also initially free, was pyrexial for 4 days after confinement with apparently the same staphylococcus present in the lochia. These infections all occurred in one corner of the ward and concerned a single group of nurses, all were type III and the usual exclusions made control of the outbreak relatively easy.

Interval. For the next 2 months, with systematic swabbing again reasonably well maintained, the department remained free from severe Grade A and B infections. Only 3 nurses had temporarily to be excluded and only occasional small spots and 'sticky' eyes occurred among the babies. There were 2 slightly inflamed breasts.

Outbreak V. Then, very early in January 1943, 3 very young babies, all in one corner of the ward, each showed numerous pemphigus lesions. All the mothers had been proved free from Staphylococcus aureus on admission. The infants' lesions all grew apparently identical Grade B strains. Re-examination of their nurses at once demonstrated a nasal and hand carrier with heavy growth of Grade B, a recently arrived pupil midwife from another hospital known to be suffering from a similar outbreak. How she came to miss preliminary swabbing is not known but the subsequent serious further extension of infection finally provoked institution of the rigid preventive routine under which the department has worked ever since. In brief it may be said of this outbreak that within a fortnight 12 more cases of pemphigus developed, 4 inflamed breasts, 1 going on to abscess, 5 cases of staphylococcal conjunctivitis of moderate severity, 1 of impetigo, and 2 of mild furunculosis in mothers. Admissions were stopped, the whole department was closed as soon as possible, sping-cleaned and restocked, and the future staff examined with great thoroughness for *Staphylococcus aureus*, Grade A and B, before a fresh start was made 3 weeks later.

Preventive Routine.

The circumstantial evidence obtained during 1942, as well as all the experiments described later in this note pointed, in our view, to four main facts:

(*a*) Active lesions are produced mainly by the more biochemically active (Grade A and B) strains of *Staphylococcus aureus*.

(*b*) These strains are mainly introduced to a previously clean department by human carriers, skin, respiratory or vaginal, temporary or permanent.

(*c*) As masks were at all times in use and in spite of them, infection spread rapidly, direct, especially hand contact must be extremely important.

(*d*) Actively handled ward equipment, bottles, etc., were readily shown to be infected and may therefore more readily pass on infection than does the ordinary ward dust which was, even during the outbreaks, surprisingly free from Grade A and B strains.

(*e*) To avoid contact spread, the routine nursing of both mother and baby, when inmates of a ward, should be guided strictly by all those principles accepted as essential in performing surgical dressings.

Therefore, besides those rules insisted upon for ordinary surgical ward technique, the following have been instituted in the maternity department since the re-opening on March 1st, 1943, and apply to the medical and domestic as well as nursing staff. With the active co-operation of the sisters and everyone concerned they have been maintained ever since. Avoidance of both entry and spread of *Staphylococcus aureus* are attempted. The same routine, has, of course, a similar effect on other pathogens such as *beta* haemolytic streptococci if the bacteriologists seek them.

We are assured by the sisters in charge that, given a full staff, to all of whom the bacteriological principles have been fully explained, and average working conditions, the routine can be carried out without undue difficulty.

1. All nurses have their nose, throat and hands cultured before commencing work in the department. All whose cultures contain Grade A or B *Staphylococcus aureus* are debarred, and they are advised simple saline irrigation of the nose, fresh air and general hygienic measures, given non-surgical and non-septic work and re-examined at intervals until free.

2. All nurses working in the department have these cultures repeated each fortnight and whenever they start colds. All growing *Staphylococcus aureus* in first plating are at once debarred but allowed to return if grading is C or D.

3. All new admissions are swabbed in respect of nose, throat, hands and vagina, or any inflammatory lesions however small. They remain in a small admission ward until the results are known, when, if negative, they join the main ward. If positive for *Staphylococcus aureus* they go to a small separation ward in which they remain for confinement and after, until the organism is graded.

4. All nurses wear masks while dealing with patients or babies and at all times in the nursery.

5. Except when absolutely necessary a baby is never handled.

6. Always before and after handling a baby or tending a recently confined mother, nurses must invariably hold their hands and forearms under a strong spray of water turned on by the foot or elbow as in a surgical theatre. They then dry on small sterile towel 'squares.' These are used only once, thrown into the basket and then laundered.

7. To reduce the handling of babies and damage to the delicate cutis of their skin and to avoid crowding in bathing, the babies are bathed as infrequently as possible, namely only at birth, when the cord separates and afterwards at intervals of 5 or 6 days.

8. After each baby is bathed, the whole of the bath and its equipment is very thoroughly washed down before being used again.

9. Each day's supply of dusting powders, olive oil, or similar applications are previously sterilized in the bacteriological department.

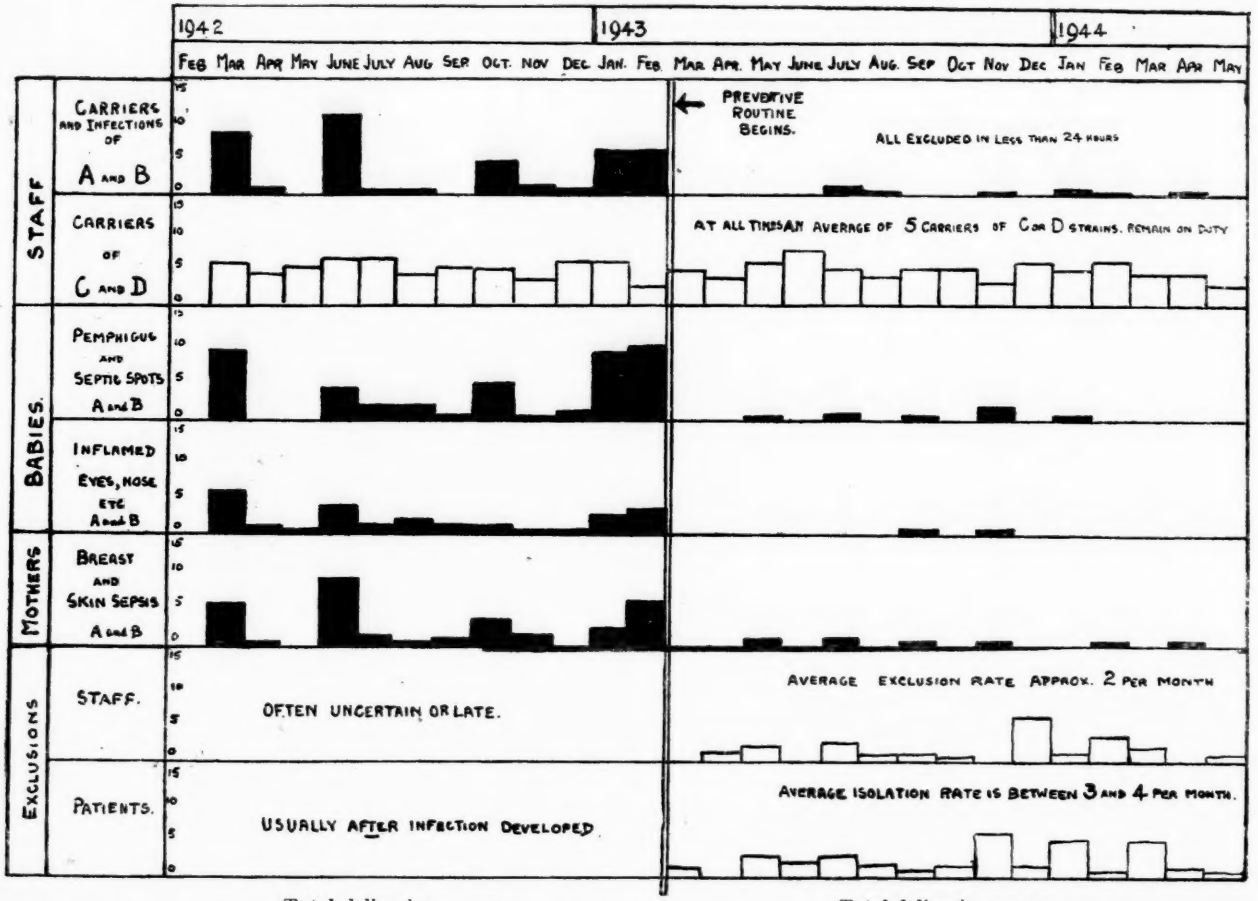
10. Only fathers are allowed to see the babies and they must wear masks. They may not handle babies. Since it is most difficult to control casual visitors to mothers their arrival is delayed until as long as possible after the confinement. Babies are not kept in the ward during visiting hours.

11. Mothers and babies infected with *Staphylococcus aureus* Grade A or B, are removed to an isolation ward away from the main department.

A Year Under Strict Routine Prevention.

If the records of 1942 and 1943 be now compared in the accompanying graph (Table IV) it will be seen that during the

TABLE IV.


1942
1943
1944
Feb Mar Apr May June July Aug Sep Oct Nov Dec Jan Feb Mar Apr May June July Aug. Sep Oct Nov Dec Jan Feb Mar Apr May
STAFF
Carriers and Infections of A and B
Carriers of C and D
BABIES.
Pemphigus and Septic Spots A and B
Inflamed Eyes, Nose etc A and B
MOTHERS
Breast and Skin Sepsis A and B
EXCLUSIONS
STAFF.
PATIENTS.
PREVENTIVE ROUTINE BEGINS.
ALL EXCLUDED IN LESS THAN 24 HOURS
AT ALL TIMES AN AVERAGE OF 5 CARRIERS OF C OR D STRAINS. REMAIN ON DUTY
OFTEN UNCERTAIN OR LATE.
AVERAGE EXCLUSION RATE APPROX. 2 PER MONTH
USUALLY AFTER INFECTION DEVELOPED
AVERAGE ISOLATION RATE IS BETWEEN 3 AND 4 PER MONTH.

Total deliveries = 225. Total deliveries = 375.

Graph illustrating distribution of carriers, secondarily infected midwives, septic staphylococcal lesions and the exclusion rates during the partially and fully controlled periods.

latter there has actually and by comparison been a marked reduction of staphylococcal septic infection. The changed conditions after the preventive routine was strictly adhered to can be illustrated even more strikingly by recording the actual number of cases of clinically significant sepsis among the mothers and babies as a percentage of the total number of confinements conducted during the period concerned (Table V). The graph does not emphasize the important point that during the 12 months of intermittent control there were only 225 confinements, whereas, ward closures and lesser interruptions having ceased, during the next 15 months 375 were dealt with, and increase of approximately 30 per cent in the effectiveness of the Department.

Graph illustrating distribution of carriers, secondarily infected midwives, septic staphylococcal lesions and the exclusion rates during the partially and fully controlled periods.
Total deliveries = 225.
Total deliveries = 375.

TABLE V.

	Intermittent control		Continuous control	
	Mar. 1942 to Feb. 1943 225 confinements		Mar. 1943 to May 1944 375 confinements	
	Number	Per cent incidence	Number	Per cent incidence
Babies:				
Pemphigus	35	15.5	1	0.27
A few septic spots	23	10.0	14	3.7
Significant conjunctivitis ...	17	7.5	6	1.5
Mothers:				
Breast abscess	4	1.7	0	0
Inflamed breast	13	5.7	6	1.5
Boils	5	2.2	2	0.35
Total infections	97	—	29	—

INCIDENTAL OBSERVATIONS.

During the period reviewed opportunity was taken, particularly at the time of the outbreaks of 1942, to make a number of direct observations on staphylococcal spread among persons and ward equipment. This detailed work is necessarily incomplete but the results already indicate, we think, a few points worthy of mention.

Equipment and Dust. Although all our direct and circumstantial evidence points to the importance of the human carrier in introducing and spreading staphylococcal infection through the Department, there is the obvious possibility that the organisms may, on occasion, first appear in dust or on equipment. To test this just over 200 direct contact and exposed plate cultures were made, approximately half during and half between the outbreaks. During outbreaks, as might be expected, we rarely failed sooner or later to grow the staphylococci from the bedding and immediate surroundings of infected persons. Of more importance were the findings during the clinically clean intervals. Was each outbreak preceded by a period of sudden increase in infections of dust and equipment? Such evidence as we have indicates that in the recorded outbreaks it was not. Weekly plate exposures and direct dust cultures were being taken at the time the first cases of Outbreaks II, III and V arose, and although isolated colonies of *Staphylococcus aureus* could be recovered from about two thirds of them, over 90 per cent of these strains clearly belonged to Grades C and D, the remaining few being only doubt-

fully B and they did not make their appearances immediately before the outbreaks. However, the point is of great importance and is now being followed up by more regular testing including the use of an air slit-sampler kindly lent to us by Dr. Bourdillon.

Cutaneous Spread in Babies. Among the 33 cases of pemphigus examined by puncture culture, the first lesion appeared at the following sites, (*a*) axillae 9, (*b*) groin and buttocks 13, (*c*) back and shoulders 6, (*d*) fingers 3 and (*e*) face or head 2. Those starting at *a* and *b* developed into the more severe cases. In all of them, when swab cultures were taken immediately from the skin surfaces up to 4 or more inches away from the initial bulla, profuse growths of a *Staphylococcus aureus* apparently similar to that in the lesions, were obtained from apparently normal areas. The moist, warm conditions between apposed surfaces evidently permitted rapid multiplication and relatively free spread when compared with the drier skin of the cheeks or back. There the area from which positive cultures could be obtained was always much more limited. In 6 cases with single initial lesions on face or shoulders, giving a pure growth of grade A organisms from the blister fluid, similar staphylococci were extremely scarce in skin swabs taken at the same time in a circle $1\frac{1}{2}$ to 2 inches away from the lesion. As might be expected, subsequent daily skin cultures proved that, in the case of the axillary and groin infections with Grade A strains, growths of similar staphylococci could, within 4 or 5 days, be obtained from almost any part of the infants' skin surfaces. The rate of spread contrasted sharply with that seen from the dry areas. Three babies with single initial lesions on face or shoulders never showed generalized skin infection although examinations were repeated at intervals during 9 days. After that all active lesions had healed. In these less severe cases some local spread could be detected, such as from face to mouth and hands or shoulders to scalp, but dispersal of infection was obviously much less.

This gradual extension of the infecting staphylococci is important in relation to routine procedures. Sooner or later in the great majority of cases, although visible lesions may not develop in these areas, the organisms reach and can be recovered from the mouth and hands. Also the less the baby is handled and towelled, the less mechanical aid will be given to the organisms in their tendency to spread.

In avoidance of skin trauma there is a further advantage. The majority of initial lesions appear at points most liable to rubbing or light abrasion. Moist areas are therefore the most vulnerable. The back, shoulders and head are specially liable to roughening by contact with garments or bedding. Minor cutaneous lesions are extremely common at the nail edges. Minute self-inflicted scratches on the cheeks are common among infants. Whenever one watches closely a series of pemphigus cases the conclusion seems inescapable that, though the arrival of an invasive *Staphylococcus aureus* on the skin is a prerequisite to the condition, nearly always it is the presence of a minute lesion of the cutis which determines the local development of the bulla. On three occasions we found that finger-pricks made in preparing a blood film from infected babies resulted next day in typical local pemphigus.

Rapid cutaneous spread may also be observed in patients not showing clinical evidence of infection. Included in our daily routine cultures were a number of babies from beds next to those of patients

who had already developed lesions and had been isolated accordingly. Clinically they were still normal but there had unquestionably been opportunity for their infection. Among 20 babies tested in this way 6 were found to carry Grade A staphylococci when their neighbours had previously shown lesions containing similar organisms. Two subsequently developed lesions and 4, all large, strong infants, did not. All the latter were isolated as soon as the presence of the organism was proved and every precaution taken to avoid the lightest injury to their skin. The existence of these few bacteriologically but not clinically infected cases is exactly what one would expect to find if the usual sequence of events were implantation of the organism on the infant's skin and general cutaneous spread followed by lesions only when its invasive powers were aided by slight local trauma or some factor causing low tissue resistance.

Spread between Infant and Mother. The hands of a mother whose infant carries large numbers of *Staphylococcus aureus* on its skin are bound to pick up the organisms. In 7 instances of Grade A infection of babies whose mothers were, before confinement, found to be free from infection, this hand contamination was easily proved. But a possibly more important form of spread was also found in each of these cases. The mouths and hands of the infant quickly transferred Grade A staphyloccoci to the nipple and breast. These mothers continued to feed their children, the two being isolated together. Repeated cultures from both gave the time relationship in spread. Within 3 to 4 days of the appearance of the first bulla on the child, the organisms could be grown from the breast surface and from the milk. Five of the mothers showed some local inflammation and in 2, small abscesses developed. In the 2 latter and 1 of the former the organism could also be recovered from a vaginal swab. None of these mothers themselves developed impetigenous or pemphigoid lesions but before all the inflammatory troubles of their infants and themselves had finally cleared, it was at one time or another possible to recover the staphylococcus from almost any part of their skin.

The slightly delayed appearance of the infecting micrococci in the milk is important in relation to the fact that *Staphylococcus aureus* may be present in the milk of a high percentage of normal nursing mothers, During our observations cultures were made from 52 samples of milk aseptically collected from 'normals.' A few *Staphylococcus aureus* were found in 36 of them (70 per cent) but none of these strains belonged to Grade A and only 3 could be classified as Grade B. Our results certainly accord with the probability that the yellow staphylococci usually met with in normal milk must belong to the less invasive strains. One might, in fact, suggest that if a Grade A or B strain is found in the milk, both child and mother should be carefully watched for inflammatory complications. We did not, however, meet among our cases any instances in which milk infection could be considered the primary source, although a few such cases may well occur.

Nasal infection of the new-born has also been suggested as an initial source of outbreaks and of spread to the mother. Again we think this sequence must be rare. We examined nasal cultures of 48 clinically normal, 2 or 3 day-old infants who had not been in even remote contact with septic cases and found that, although 12 (25 per cent) gave some colonies of Staphylococcus aureus all belonged to C or D strains. No grade A or definitely B strain was ever grown from an infant who, for certain, had not been in contact with infection.

Conclusions.

As a result of systematic observation of the cases in an obstetric department over a period of 2 years and 3 months, evidence is brought forward that:

(1) The *Staphylococcus aureus* giving rise to epidemic infections is very frequently introduced by previously unsuspected human carriers among either patients or staff.

(2) Bacteriological recognition of these carriers and also of the spread of the micrococci which they introduce can to a large extent be achieved by grading the staphylococci by cultural methods, the relative simplicity of which, even if it results in a few unnecessary exclusions, obviates delay and allows the immediate adoption of isolation and barrier precautions without which outbreaks cannot possibly be brought to an end quickly.

(3) Particular attention having been drawn to the spread of *Staphylococcus aureus* infection in pemphigus neonatorum, the primary importance of hand and other forms of direct contact are in this connexion specially emphasized.

(4) So as to prevent or at least greatly reduce the chances that invasive *Staphylococcus aureus* will gain access to the department, or, having entered, result in an epidemic infection, a preventive routine is essential. A suggested scheme which has worked well for over a year is given in detail.

(5) Continuous bacteriological control in a maternity department far exceeds in value *intermittent* bacteriological testing, and does not involve a prohibitive amount of work or number of exclusions.

(6) It is evident that in the design of maternity hospitals and departments, provision should be made for:

(i) A small admission ward or wards for the detention of patients until they are shown to be bacteriologically 'clean' and can be admitted to the main wards.

(ii) Adequate separation or observation wards for the segregation of patients who are 'suspect' bacteriologically, until all organisms present have been assessed as harmless.

(iii) Isolation beds away from the main buildings, if possible, for the reception of patients shown to be carrying pathogenic organisms, but who are not seriously septic.

(iv) Isolation beds for seriously septic cases.

In connexion with the numerous circumstantial and routine bacteriological observations upon which these notes are based, often adding appreciably to the trials of an already hard-pressed staff, we wish particularly to thank Sister D. Jackson, Ward Sister in Charge, for her invaluable and most ready co-operation. We are indebted to Mr. A. R. Hines for much painstaking laboratory work, and to the successive Resident Obstetricians, Mr. H. A. Ripman, Mr. T. L. T. Lewis, Mr. R. Ticehurst and Mr. A. R. Williams for their unfailing interest and great helpfulness.

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Treatment of Amenorrhoea with Combined Anterior Pituitary Follicle-stimulating Hormone and Chorionic Gonadotrophin

BY

ALBERT DAVIS, M.D., Ch.M., F.R.C.S.

Consultant Obstetrician and Gynaecologist, L.C.C., etc.

EXPERIMENTAL evidence tends to prove that a combination of chorionic gonadotrophin and pituitary follicle-stimulating hormone is considerably more potent as a gonadal stimulant than either of its individual constituents. In experimental animals it produces precocious follicle maturation, and it is capable of stimulating growth in the atrophied ovaries of hypophysectomized rats (Evans *et alia*[1]), Relatively little is known concerning the action of this drug in the human subject, and it was with the object of elucidating its value that the present investigation was undertaken. The condition which appeared most likely to benefit from this new form of combined therapy was amenorrhoea, and accordingly, 27 patients of the secondary pathological type were treated by routine injection over periods varying from 6 months to 1 year, the clinical results being supplemented in many of the patients by repeated endometrial biopsy. The combination has recently been produced commercially under the name of "Synapoidin," and this abbreviation will be used throughout.

RATIONALE.

The highest known link in the endocrine chain which controls menstruation is the anterior pituitary. (There is some evidence that a higher centre might exist in the hypothalmus (Hohlweg[2]) and the well known effect of psychological disturbance on the menstrual cycle is proof of some sub-cortical influence, but until adequate experimental evidence is forthcoming the presence of such primitive "sex centres" must remain largely hypothetical). The precise nature of this pituitary mechanism has not been completely elucidated, but basically the gland exerts its influence by producing two hormones, one which stimulates follicular growth and another which produces ovulation and luteinization (Zondek[3]). Thus, injection of anterior lobe extracts into immature animals provokes the premature production of the whole cycle of oestrus, i.e. ovarian follicle growth with maturation of the ovum and secretion of oestrogen, followed by ovulation, luteinization, and the production of progesterone. The same treatment given to hypophysectomized animals, which normally do not show ovarian changes, produces similar results. In the human female the sexual cycle is likewise completely dependent on the integrity of the gland, and when it is destroyed, either surgically (Elden[4]) or pathologically, as in Simmonds's disease, complete suppression of the menses follows.

The pituitary hormones, on account of

the smallness of the parent gland and its low storage threshold, are difficult to obtain in satisfactory quantity for therapeutic purposes. Similar substances, however, are present in the serum of pregnant mares and in the urine of pregnant women, from both of which they can be extracted in considerable amount. Neither of these anterior pituitary-like gonadotrophic hormones, however, are identical with their precursors in the parent gland, particularly in relation to their comparative effect on animals and human ovaries. That derived from equine pregnancy serum, for example, while as effective as pituitary gonadotrophin in experimental animals, is considerably less so in the human. Similarly chorionic gonadotrophin, which reproduces in most animals all the changes caused by the luteinization hormone of the pituitary is apparently quite inactive in the case of monkeys and, probably, women. These differences account for many of the discrepancies between laboratory tests and clinical results, and they must constantly be borne in mind in the application of commercial extracts to the treatment of hormone deficiency syndromes in the human.

The immediate control of the menstrual cycle is exercised by the hormone of the maturing unruptured follicle (oestrogen) and that of the corpus luteum (progesterone) and it is the co-ordinate and complementary action of these agents which directly initiates menstruation. But it is the anterior pituitary which plays the pivotal role, for its gonadotrophic principles, by stimulating ovulation, provide the initial impetus for the production of both ovarian hormones. The whole ovarian cycle of follicular growth, ovulation, and luteinization, together with its external menstrual manifestation, is thus "totally dependent upon the successive and integrated action of the two pituitary sex hormones" (Mazer[5]), and functional menstrual disorder of any kind must therefore be primarily ascribed to some disturbance of this delicately synchronized pituitary rhythm. Thus hyperactivity and incoordinate action of the gland is manifested in metrorrhagia, metropathia haemorrhagica, follicular cystic disease, and similar "excess syndromes," while functional pituitary deficiency is the commonest cause of pathological amenorrhoea.

It is apparent, therefore, that the therapeutic approach in a case of functional amenorrhoea should be by way of treatment with pituitary or pituitary-like gonadotrophins rather than by substitution therapy with oestrogen and/or progesterone. This view is reinforced by the uncertain and transitory effect of ovarian treatment, and by the possibility of reflex pituitary depression, a phenomenon which Hohlweg[2] has shown to follow the administration of oestrin in large doses. It has, unfortunately, been found impossible to produce pituitary extracts in sufficient concentration to ensure adequate ovarian stimulation in the human, and until these are obtainable primary therapy must remain ineffective. In addition, chorionic gonadotrophin is clinically useless in amenorrhoea. A curious synergy, however, has been discovered between these weak pituitary extracts and chorionic gonadotrophin, and the reinforcement so produced is sufficiently strong to render unnecessary further concentration of the former. The mechanism of this synergy is obscure, for both factors involved are individually ineffective; further, the presence of gonadotrophin in the pituitary fraction appears unnecessary (Evans[6]). The most powerful combination, however, is one in which the pituitary follicle-stimulating hormone predominates, and this, prepared under the trade name Synapoidin, is the one I have used throughout.

Classification.

For clinical purposes we have classified our cases of amenorrhoea according to the organ the failure of which is presumed to be primarily responsible. This may be the pituitary, ovary, uterus, thyroid or adrenal, and although a certain amount of overlap is inevitable, most patients will fall into one or other of these groups.

1. *Amenorrhoea of Pituitary Origin.*

(a) *Functional pituitary deficiency.* Most amenorrhoea patients show signs and symptoms comparable to those of a very mild case of Fröhlich's syndrome, and as the fully developed disease is known to be due to a functional pituitary disorder it may be assumed that its slighter manifestations are of the same origin. These are principally adiposity and genital hypoplasia. The excess fat is deposited characteristically in the lower abdomen, thighs and breasts, and the increase in bust and hip measurements is often considerable. Genital hypoplasia is shown in the results of the secondary ovarian suppression. Thus the uterus is diminished in size, with scanty endometrium, the ovaries show delay or absence of follicle maturation, and the urine oestrogen content is below normal. The thyroid is often diffusely enlarged and the basal metabolic rate is low.

(b) *Organic pituitary disease.* Necrosis of the anterior lobe (Simmonds's disease) is marked by a wasting cachexia and amenorrhoea. It is occasionally caused by an infected embolus of pelvic origin, and the one case in my series was attributable to a severe puerperal sepsis. The fully established disease is rare, but milder degrees are relatively common and this pathology probably explains the sequence of events in some patients who complain of lassitude, loss of weight, and amenorrhoea following a septic abortion or delivery. Of the pituitary adenomas the chromophobe and basophilic types produce amenorrhoea and obesity, associated in the former case with compressive ocular signs.

2. *Amenorrhoea of Ovarian Origin.*

Some authorities describe a symptom-complex of primary functional deficiency of the ovaries, characterized by amenorrhoea, disproportionate limb length and genital hypoplasia. Such cases are frequently seen but it is probable that the majority as shown above are of primary pituitary origin, the ovary playing its more usual secondary distributive *rôle*. Destructive lesions of the ovary do, however, account for some cases of amenorrhoea. These include tuberculosis, and some adenomata, but then only occasionally do these conditions cause complete menstrual suppression, for the smallest fraction of functioning ovary is capable of maintaining the sexual rhythm. Hypomenorrhoea, however, is a not uncommon sequel years after a severe adnexitis, probably because the amount of oestrogen secreted by the depleted ovary, while sufficient to stimulate menstruation, is inadequate to maintain the pituitary-ovary-pituitary cycle. Four of the cases in my series come under this heading. Certain specific ovarian tumours (arrhenoblastoma and dysgerminoma) may cause amenorrhoea, the former by excessive androgen production, but both are rare. In one of my patients the ovaries had been inadvertently damaged during X-ray treatment for osteoarthritis following hip dislocation, and I have also seen several patients in whom over-dosage of X-rays for menorrhagia had produced the same result.

3. *Amenorrhoea of Uterine Origin.*

This may follow destruction of the basal endometrium by acute endometritis,

too thorough curettage, or the intrauterine application of caustics. The condition, though uncommon, is by no means rare, and may be diagnosed by the presence of normal serum- and urine-hormone levels, with an atrophic endometrium on curettage. Occasionally one encounters a woman whose endometrium shows all the normal cycle changes except for the monthly loss. This syndrome has been ascribed to the absence of the so-called specific endometrial bleeding factor, but its exact mechanism is still largely hypothetical.

4. *Amenorrhoea of Adrenal Origin.*

Adrenal tumours cause amenorrhoea through their excessive secretion of androgens. Masculinization is more or less marked, with hirsutes and voice changes. Simple hyperplasia of the gland results in slight symptoms of the same direction, but these are always sufficiently apparent to point the correct diagnosis.

5. *Amenorrhoea of Thyroid Origin.*

Thyroid deficiency, particularly when the gland is enlarged, often causes menstrual suppression, though this is by no means invariable. Amenorrhoea is also, paradoxically enough, very common in Graves's disease, occurring in about 50 per cent of all cases.

6. *Other Causes of Amenorrhoea.*

There is a widespread belief that anaemia is a common cause of amenorrhoea, but this is very rarely the case. The menses are normal with quite severe anaemias and a girl must be chlorotic before they are suppressed. I have seen only one case during the past year in which the symptom was attributable solely to this cause. Menstruation is also suppressed in chronic wasting diseases, and in some organic nervous affections.

CLINICAL MATERIAL.

Twenty-seven consecutive cases of pathological amenorrhoea were submitted to complete clinical and laboratory investigation, and treated systematically with Synapoidin alone, generally with repeated biopsy control. The dosage used was 1 c.c. (15 "synergy rat-units") in all cases, given intramuscularly 3 times weekly for 3 weeks, providing haemorrhage did not supervene or that the ovary did not enlarge unduly during the administration. (One synergy rat unit is the minimal total quantity which when injected subcutaneously, in equally divided doses, twice daily for 3 days into normal immature rats, provides in that time an average ovarian weight 5 times that of untreated controls.) This is twice the dosage originally recommended by Mazer,[5] but I have found the smaller amount relatively useless, and with careful supervision any untoward manifestations are easily controlled by immediate withdrawal of the drug.

Treatment was not commenced, however, until the precise cause of the amenorrhoea was determined as definitely as possible in each case by routine investigation. This included general systemic investigation, estimation of the basal metabolic rate, X-ray examination of pituitary fossa, diagnostic curettage and lipiodol hysterography, and it was then fairly easy to classify each case into one of the groups discussed above. In 19 the amenorrhoea was of primary pituitary origin, in 6 it was the direct result of ovarian destruction, and in 2 the thyroid was at fault.

The majority of the patients were of the primary pituitary type showing the characteristics of a mild Fröhlich syndrome, and the following case history is typical of most:

CASE 1. S.M., married, age 31, 1 child, 5 years old. Menarche 14. Menses were regular 5/27 until

March 1942, since when only slight, irregular losses at 10 to 12 weekly intervals for 1 day. Considerable recent increase in weight, flushes, lassitude, and sterility. Examination on May 6th, 1942, revealed male type of hirsutes, obesity of Fröhlich type, B.M.R., 70 per cent, hypoplasia of uterus and scanty atrophic curettings. Thyroid not enlarged and pituitary fossa normal. A complete course of Synapoidin did not produce any haemorrhage, but examination showed considerable increase in size of the uterus and right ovary, with premenstrual type of endometrium. A considerable loss followed 2 more injections and the patient has menstruated every 28 days since, the period lasting 3 days, with copious loss. She is also getting appreciably slimmer, although the hirsutes remains. Libido was unaffected throughout. Recent curettings showed a normal secretory stage endometrium corresponding to the correct phase.

The rapidity and apparent permanence of the cure in this case is by no means characteristic of all, but as a general rule those patients exhibiting similar features did extremely well, thus verifying the hypothesis of a primary pituitary origin.

Occasionally a patient with amenorrhoea due to this cause may, paradoxically, lose weight, though the Synapoidin reaction is proof of pituitary deficiency.

Case 2. J.L. Seen April 14th, 1941. Married 4 years, age 28. Periods regular 4/28 until February 1941. Since that time she has lost weight steadily and there is complete absence of libido (previously strong). Routine examination showed an emaciated but otherwise apparently healthy girl. Uterus extremely hypoplastic and curettings almost unobtainable. June 16th, 1942. No effects following oestrin-progestin replacement (Kauffman technique). August 11th, 1942. No effect from thyroid-oestrin therapy. February 14th, 1943. No effect following subcutaneous oestrin-progestin implantation plus anterior pituitary-like gonadotrophin. April 21st, 1943. Similar negative results from full course of Synapoidin in ½ c.c. doses. November 6th, 1943. Patient had 2 severe losses at 6-weekly intervals following course of Synapoidin 1 c.c. Examination shows considerable increase in size of the uterus. There is, however, no increase of sex feeling and no weight increase.

The superiority of this method of treatment over replacement therapy in primary ovarian deficiency, even when the latter is extreme, is well illustrated in the following history:

Case 3. Miss D.H., age 27. Seen originally February 27th, 1940, complaining of severe menopausal symptoms following accidental sterilization by X-rays during treatment for arthritis due to bilateral congenital hip dislocation 6 years previously. No periods since, though libido present and sex relations normal. Examination showed a tiny uterus and impalpable ovaries. June 11th, 1940. Excellent symptomatic result following a course of intra-pelvic diathermy with production of 2 normal periods. Recurrence of symptoms and amenorrhoea, however, after 2 months. July 9th, 1942. One period of anovular type produced by one course of combined oestrin-progestin replacement therapy. This was not repeated spontaneously though the uterus was appreciably increased in size. December 29th, 1940. A further similar slight "period" produced by another replacement course. March 28th, 1941. A similar bleeding after subcutaneous implantation of oestradiol benzoate 30 mg. and proluton 25 mg. but again this was not repeated spontaneously. March 3rd, 1943. Three 4-day periods at 3 to 6 weekly intervals produced by full course of Synapoidin. September 14th, 1943. Irregular periods since at 6 to 8 weekly intervals.

Three similar patients in whom ovarian function had been diminished to the amenorrhoea level by inflammatory destruction (R.M.), partial operative removal (O.R.) and cystic degeneration (A.T.) were similarly benefited by Synapoidin, after replacement therapy had been unsuccessful. In one, however, although the endometrial picture is apparently normal, the periods fail with cessation of treatment, which has had to be repeated monthly. (This impermanency has been a common feature of our cases). Paradoxically an

almost identical case (M.L.) with amenorrhoea due to bilateral tubo-ovarian abscesses, did not show any result whatever from Synapoidin, though fairly regular periods, some admittedly anovular, followed oestradiol implantation and oestrin by mouth. She has since become pregnant.

Complications.

None of our patients have shown any of the allergic reactions recently reported from America, and the drug is apparently free from adverse general effects in the majority of cases. Excessive bleeding was noticed in 3 cases, but this, though initially alarming, was transitory, and was repeated spontaneously in only one. A more serious complication is gross enlargement of the ovary. This is also more frequent for it occurred in 6 of our patients. The increase in size is due to multiplication of the corpora lutea and haemorrhagic follicles, with much oedema and interstitial haemorrhage, and occasionally (case 16) large single cyst formation. The growth is usually rapid and often considerable, the ovary in one of our cases developing to the size of a large lemon in 6 weeks. Involution is correspondingly slow, and it usually takes several months for the organ to resume its normal size

The clinical significance of this enlargement is difficult to assess for it is generally painless, being only discovered by routine examination, and it resolves spontaneously in most cases. But apart from the indication they give of overdosage, such tumours are obviously liable to the general risks of complications such as haemorrhage, torsion, etc., and so call for careful supervision during treatment.

Results.

This series is a relatively small one, and several different types of cases are included, so that accurate assessment of results is difficult. Taken *en masse* the figures show an apparently permanent cure-rate (i.e. restoration of normal menstrual rhythm for at least 6 months), in 14 of the 27 patients, temporary improvement in a further 6, without any results in the remainder. The type of patient found most likely to benefit from Synapoidin therapy was the mild Fröhlich hypopituitary, particularly when increase in weight was fairly marked. (This latter factor is significant, for when it was absent the results were usually poor.) The reaction of other cases varied with the degree of pathological change in the organs concerned. The time factor was of relatively little significance, for if a patient were benefited the duration of previous amenorrhoea did not seem to affect the result. A further point of interest is that in 6 cases, though the initial result was excellent, it was not maintained spontaneously, so that menstruation in these cases is entirely dependent on repeated courses of Synapoidin.

Comment.

In Synapoidin we have a preparation considerably superior in action to previous therapeutic combinations. Its chief value is in the treatment of amenorrhoea of pituitary origin, but it has a definite, though less certain, action in other types. Unfortunately absolute differentiation of the various causes of amenorrhoea by ordinary clinical and laboratory methods is by no means certain, so that paradoxical results are common, and until a clearer diagnostic technique is available it is justifiable to use the drug more or less indiscriminately in these cases. It cannot, however, be too strongly emphasized that it should be employed only after the most careful general examination has failed to reveal gross abnormalities of the type discussed

above, and such examination must be repeated frequently throughout the course of treatment to control ovarian hypertrophy. In addition, haemorrhage, however slight, is an absolute contraindication to continuance of the treatment.

I am indebted to Messrs. Parke Davis & Co., the manufacturers, through Dr. Stanley White, for generous supplies of Synapoidin.

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Premature Birth

(Analysis of 1,000 Cases)

Incidence, Aetiology, and Immediate Result to the Baby

BY

S. C. SANDIFER, M.B., B.S., Surgeon Lieutenant, R.N.V.R.

Late Senior Resident Medical Officer, Queen Charlotte's Maternity Hospital, London.

THE Statistical Review of the Registrar-General for England and Wales[1] states that during the year 1938 there were 24,729 stillbirths, 17,572 infant deaths in the first 4 weeks of life, and a total of 621,204 live-births. Analysing this neonatal mortality, the Review shows that "Premature Birth" was the certified cause of death in just over half these cases, being responsible for 8,984 neonatal deaths, or 14.47 deaths per 1,000 live-births, the total neonatal mortality rate being 28.29 per 1,000 live-births. Premature birth was probably responsible, indirectly, for many additional neonatal deaths, for, as McNeil[2] has stated, prematurity does not in itself cause death, but allows the main lethal factors of the neonatal period to act with multiplied power. Thus, many cases certified as "Atelectasis," "Intracranial Haemorrhage," for instance, may in reality be the result of premature birth, and the figure 8,984 deaths must represent the very minimum. No other cause of death gave such a large figure: for example, Congenital Malformations caused 3.73, Birth Injury 2.52, Atelectasis 1.87, and Pemphigus Neonatorum 0.57 deaths per 1,000 live-births.

The percentage of stillbirths associated with premature birth has been given as 50.7 per cent (McNeil[2]) and 52.9 per cent (Potter and Adair[3]). From these figures, at least 12,400 stillbirths were associated with premature birth, although not necessarily due to the premature birth.

The smallest total representing the natal and neonatal mortality associated with premature birth for the year 1938 is thus 21,400, or 33.1 per 1,000 total births. This total was more than the numbers of deaths in that year certified as due to "Disease of the Coronary Arteries" (17,182), and "Old Age" (15,325); almost as many as the deaths due to "Tuberculosis of all Forms" (26,176), and death from "Violence" (22,780), and, finally, it was just under one-third of the Cancer death-rate.

A significant reduction of neonatal mortality and stillbirth could be brought about by reduction of the incidence of premature birth. Whether this can be achieved, with the existing state of medical knowledge, at first sight appears most uncertain.

The information regarding the nature and cause of the onset of normal mature labour is very vague and limited. Clinical experience, however, teaches that premature labour is often associated with some abnormal condition of the mother or foetus, this association being more constant in premature birth than in mature birth. Many other factors must be involved however, because the presence of the abnormality during pregnancy does not necessarily result in a premature birth, although it would seem to predispose to it.

An analysis of 1,000 cases of premature birth has been made to prove the accuracy of this statement, and, at the same time provide statistical *data* from which it may be possible to determine in what direction lies any hope of prevention or reduction of the condition. The analysis is based on a consecutive series of births occurring in Queen Charlotte's Maternity Hospital from April 1936 to December 1942. The definition of premature birth adopted in this series follows the recommendation of the League of Nations Medical Committee—birth weight of $5\frac{1}{2}$ pounds or less, occurring after the 28th week of pregnancy.

Incidence.

During the period under consideration, 12,323 births after the 28th week of pregnancy occurred in the hospital, the 1,000 premature babies representing 8.11 per cent of this number.

Premature births and "booked" deliveries numbered 781, and occurred in a total of 11,518 "booked" deliveries, representing a "booked" premature birth-rate of 6.78 per cent.

"Emergency" deliveries amounted to 219 of the premature births occurring in a total of 805 "emergency" deliveries, representing an "emergency" premature birth-rate of 27.2 per cent.

Of the 781 premature "booked" births, 190 were the result of induction of premature labour, giving a corrected or spontaneous "booked" premature birth-rate of 5.13 per cent.

Aetiology.

The 1,000 cases were found to be distributed among three groups: (*a*) premature birth, cause unknown, 372 cases; (*b*) premature birth, as the result of induction of premature labour, 319 cases; (*c*) premature birth, associated with abnormal maternal or foetal conditions but not induced, 309 cases.

(A) *Cause Unknown.*

This group comprised 372 of the total number of cases, or 37.2 per cent. Definite cause for the premature labour could not be found, and there was not any associated maternal or foetal abnormality.

These cases were distributed in the following weight groups:

Table I.
Cause Unknown.

Weight in pounds	Numbers of cases
5 to $5\frac{1}{2}$	139
$4\frac{1}{2}$ to 5	97
4 to $4\frac{1}{2}$	54
$3\frac{1}{2}$ to 4	32
3 to $3\frac{1}{2}$	22
$2\frac{1}{2}$ to 3	11
2 to $2\frac{1}{2}$	10
Under 2	7

(B) *Premature Birth—Induced.*

Labour was induced prematurely in 319 cases, that is 31.9 per cent of the total premature births.

A detailed analysis of the reasons for induction with the number of cases in each weight group in the "induced" series is given in Table II.

Although other obstetric complications were present in some of these patients, mention of this is not made. The premature birth was due to the induction and each case is thus classified according to the indication for the induction.

(C) *Premature birth—Labour not induced.*

This group of cases included all those premature births in which the onset of labour was spontaneous, but associated with some definite maternal or foetal condition in every case.

There were 309 such births or 30.9 per cent of the 1,000 cases.

Table III gives a detailed analysis of these spontaneous cases.

Overall Results of the 1,000 Cases.

The survival-rate, i.e., discharged and apparently healthy, but often before 28 days, of the whole of the premature births was 60.4 per cent. The stillbirth-rate was 25.2 per cent; 14.4 per cent of the babies died after birth before discharge from hospital.

Routine postmortem examinations were carried out on the babies born dead and on those that died, during the first 4 years of this series, but owing to the shortage of medical staff since the war this has not

Table II.
Labour Induced.

Pounds	5–5½	4½–5	4–4½	3½–4	3–3½	2½–3	2–2½	Under 2	Total
Toxaemia of pregnancy, including essential hypertension	45	38	27	34	28	16	9	8	205
Placenta praevia	7	7	4	1	3	5	2	1	30
Accidental antepartum haemorrhage	6	2	2	4	2	3	0	1	20
Eclampsia	2	0	2	5	3	2	2	0	16
Disproportion	9	4	3	0	0	0	0	0	16
Foetal abnormality	5	1	0	4	1	3	0	0	14
Pyelitis of pregnancy	1	2	0	0	0	0	1	0	4
Hyperemesis gravidarum	0	0	1	1	2	0	0	0	4
Hydramnios (foetus normal)	1	1	0	0	1	0	0	0	3
Chronic nephritis	0	0	0	1	1	0	0	0	2
Unstable presentation	2	0	0	0	0	0	0	0	2
Heart disease	1	0	0	0	0	0	0	0	1
Uterine fibroids	0	1	0	0	0	0	0	0	1
Mental condition	0	1	0	0	0	0	0	0	1
Totals	79	57	39	50	41	29	14	10	319

Table III.
Spontaneous Premature Labour.

Pounds	5–5½	4½–5	4–4½	3½–4	3–3½	2½–3	2–2½	Under 2	Total
Multiple pregnancy	61	37	37	20	13	4	6	0	178
Toxaemia of pregnancy, including essential hypertension ...	12	6	5	5	3	1	2	4	38
Accidental antepartum haemorrhage ...	4	5	2	3	4	6	2	2	28
Foetal abnormality	1	1	5	3	1	2	5	0	18
Placenta praevia	3	2	5	1	0	1	1	0	13
Hydramnios (foetus normal)	2	0	2	3	1	0	1	0	9
Eclampsia	2	1	2	0	0	1	0	0	6
Pyelitis of pregnancy	1	0	2	1	0	0	0	0	4
Accident or injury to the mother ...	0	1	0	0	3	0	0	0	4
Antenatal version	2	1	0	0	0	0	0	0	3
Hyperemesis gravidarum	1	1	1	0	0	0	0	0	3
Heart disease	1	1	0	0	0	0	0	0	2
Uterine fibroids	1	0	0	0	0	0	0	0	1
Acute appendicitis	0	1	0	0	0	0	0	0	1
Syphilis	0	0	1	0	0	0	0	0	1
Totals	91	57	62	36	25	15	17	6	309

been done in all cases recently. It is unlikely, however, that this would alter the results to any great extent.

The analysis of the total numbers of cases in each weight group, with the "stillborn," "living" and "died" numbers in each weight group, is found in Table IV.

(1) Firstly, some explanation of the Tables may be necessary. In some cases more than one associated condition was present, for example, multiple pregnancy with toxaemia, and toxaemia with accidental antepartum haemorrhage. These cases have been classified according to the immediate cause of the premature birth, twins induced for toxaemia appearing as 2 premature births induced because of toxaemia and not as a case of multiple pregnancy; cases of toxaemic antepartum haemorrhage do not appear under the heading of toxaemia; twins born after spontaneous labour appear as 2 cases in the "Spontaneous Premature Birth" group. Even so, it is doubtful if the results, taken as a whole, are essentially different from those of comparable series of cases of premature births.

TABLE IV.

Immediate Results of Prematurity.

Pounds	Total	Discharged alive	Died in hospital	Stillborn	Natal and neonatal death-rate
5 to 5½	309	246	20	43	20.4 per cent
4½ to 5	211	167	11	33	20.8 ,, ,,
4 to 4½	155	104	22	29	44.4 ,, ,,
3½ to 4	118	51	31	36	56.8 ,, ,,
3 to 3½	88	25	27	36	71.6 ,, ,,
2½ to 3	55	9	15	31	83.7 ,, ,,
2 to 2½	41	2	15	24	95.1 ,, ,,
Under 2	23	0	3	20	100.0 ,, ,,
Totals	1000	604	144	252	39.6 ,, ,,

(2) The prematurity-rate for all cases was 8.11 per cent; for booked cases receiving full antenatal supervision, either as out-Patients or as in-Patients, it was 6.78 per cent; and when induced cases were excluded this rate fell to 5.13 per cent. Thus it would appear that in spite of full supervision and non-interference, approximately every 20th birth will produce a premature baby. McNiel,[2] using the same standard of prematurity, has estimated the incidence of premature birth at the Edinburgh Royal Infirmary (for all cases) at 12 per cent, with a provisional estimate of 10 per cent for Scotland as a whole. Potter and Adair[3] from the Chicago Lying-in Hospital gave a rate of 5.8 per cent of live-births only, and used as their standard the possession of two of the following characteristics: Weight 5½ pounds or less, length 47 cm. or less, or gestation period less than 37 weeks. Baird[4] has given the incidence of "premature labour" as 9 per cent in booked hospital cases from working class patients in Aberdeen, 6 per cent in upper and middle class patients, and 2 per cent in booked specialist cases, these latter cases showing relatively little incidence of toxaemia, few cases of contracted pelvis and little anaemia or malnutrition. Similar reports are available designed to show the influence of the maternal diet during pregnancy upon vari-

ous obstetric complications. Ebbs *et al*[5] from Toronto showed a prematurity-rate of 8 per cent for mothers having a "poor" diet during pregnancy as against 3 per cent in mothers having a "good" diet. The figures of this report, however, do not appear to be beyond statistical reproach, and the authors do not state their standard of premature birth.

The London Experiment[6] along the same lines reported by the Peoples' League of Health was better controlled and well analysed statistically, and dealt with two equal series of pregnant women, on given supplementary Iron, Calcium, Iodine, Manganese, Copper, and Vitamins A, B, C and D, the other group having their normal diet. The report gives the incidence of premature birth (birth before 40th week) in untreated primigravidae as 23.9 per cent and in treated primigravidae as 20.1 per cent, the corresponding figures for multigravidae being 24.2 per cent and 20.1 per cent respectively. The figures do not represent the number of premature babies and it is unfortunate that the figures are based on such a vague factor as the period of gestation. It is interesting to recall that some premature babies are born at term. James Young[7] has stated that, at the British post-Graduate Medical School, London, during the years 1937 to 1942, the incidence of premature birth had declined from 19.7 per cent to 14.2 per cent in booked primigravidae and from 16.7 per cent to 13.6 per cent in booked multiparae.

Whatever the incidence of premature birth in all these hospital series of cases may be, it will obviously be higher than in obstetric practice generally because of the large number of emergency deliveries, these cases having a prematurity-rate of 27.2 per cent at Queen Charlotte's Hospital against 6.78 per cent for booked cases, including cases induced in both series.

(3) Toxaemia and multiple pregnancy were together responsible for 443 premature births (44.3 per cent), toxaemia causing 265 and multiple pregnancy 178. Antepartum haemorrhage caused 91 premature births. One fact is strikingly obvious from the results in the Tables, that the vast majority of the cases with some definite cause had an obstetric cause, non-obstetric associated conditions being rare —syphilis, accident or injury, and heart disease—the incidence of these conditions being no higher in cases of premature birth than in mature birth. An example of this is seen in cases with heart disease, where the incidence of this in the 11,323 mature births was 1.2 per cent and in the 1,000 births (premature) 0.3 per cent. But when considering the obstetric conditions present there is a much higher incidence in cases ending in premature birth. It is not possible to form accurate estimations of this by comparing the numbers of the various associated abnormalities in the 1,000 premature and 11,323 mature births because of the higher percentage of emergency cases in the 1,000 prematures, these emergencies having, as we have seen, a high premature birth-rate (27.2 per cent and almost 100 per cent associated abnormality-rate.

However, by considering booked cases only, and dividing them into two groups—premature and mature—the following definite figures can be obtained:

TABLE V.

	Mature Per cent	Premature Per cent
Toxaemia	4.3	21.9
Twins	1.8	16.9
Antepartum haemorrhage	0.7	6.6

(4) Table IV is of interest in that, for this series, it shows a natal and neonatal death-rate for even the biggest premature

babies of 20.4 per cent and a total mortality for the whole group of 39.6 per cent. From this figure and the Statistical Review[1] for 1938 (a year in the period under consideration) a rough estimate of premature birth for England and Wales may be obtained —33,500 cases—representing a total prematurity-rate of approximately 8 per cent.

In the 12,323 total births there were 622 stillbirths, and of these, 252 were premature foetuses, or 40.5 per cent of the hospital stillbirths were premature. In the same total there were 308 infant deaths in hospital, of which 144 were premature babies, or 46.7 per cent of the infant deaths.

The Statistical Review[1] gives neonatal mortality-rates per 1,000 live births due to "Premature Birth" for various parts of the country. In greater London this was 11.47, South Wales 16.41, and Durham and Northumberland 17.17. Corresponding stillbirth-rates (per 1,000 total births) were 31.51, and 39 respectively, presumably about 50 per cent of these being associated with prematurity. The probable significance of these figures will be discussed under the next heading.

There is little information available regarding the relation of premature birth to stillbirth (McNeil,[2] and Potter and Adair[3]) but more has been written about the connection with neonatal death. Some paediatricians have succeeded in reducing the neonatal mortality-rate of these babies to very low levels.

In Chicago, Barnes and Wilson,[8] in two consecutive series of babies, reduced the mortality from 32.5 per cent to 9.5 per cent, using all available equipment and special technique. Lamb[9] similarly reduced the rate from 27.07 per cent to 8.33 per cent in New York. In London, Field,[10] using less impressive methods, reported a mortality of 8.1 per cent.

Conclusions.

The problem of premature birth, although at first sight formidable, is capable of solution by two methods. The first of these is concerned with prevention of the premature birth, the second with the treatment of the premature baby after failure to prevent the labour.

(a) *Prevention of Premature Birth.*

Consideration of the first group (A) of 372 cases—cause unknown—probably reveals the most hopeful field for future investigation. It seems highly probable that social conditions and status, together with the quality of the antenatal diet, play a large part in the production of these cases. It is important that further investigations should be carried out on these lines, as in the case of pulmonary tuberculosis in the population as a whole, using more definite standards of diet and social status than have been adopted in the few investigations so far performed, and remembering that the terms upper and middle class and "good" diet, are not synonymous. However, from the work of Ebbs *et al*[5] and the London Experiment,[6] it is seen that a definite and significant reduction can be achieved by the use of supplemented diets. Another great help would be the provision of a domestic help service for the last 6 weeks of pregnancy, so that adequate rest and freedom from worry could be obtained for every expectant mother. At present, help is available after the birth of the child, but surely it is just as important during the last 4 to 6 weeks of pregnancy. The problem of these 372 cases does not seem quite so formidable as at first sight.

The 628 cases with a definite cause—groups B and C—present a more difficult problem, and these types of cases will probably remain the hard core of prematurity. Many of these cases are definitely

unpreventable, such as the gross foetal abnormalities, and, for practical purposes, accidental antepartum haemorrhage, but for the majority some improvement could be obtained.

The incidence of toxaemia, causing 265 premature births, can be reduced by supplementary feeding, as shown by the London Experiment, from 6.42 per cent to 4.51 per cent in primigravidae. The provision of domestic help would probably reduce this a little more. Then, larger numbers of antenatal beds in Maternity Hospitals for the cases with early toxaemia would probably prevent the necessity for an appreciable number of inductions of premature labour, assuming that these inductions are already used intelligently. Twins might be saved the hazards of premature birth by prolonged maternal antenatal rest in bed, in hospital if necessary, for the last 6 to 8 weeks of pregnancy. Placenta praevia treated by means of Caesarean section would give its associated premature babies a better chance of survival, but perhaps more mature babies might be produced by non-interference and watchful inactivity unless, of course, the state of the mother did not warrant this.

The key to this part of the problem appears to be, in view of existing knowledge, adequate antenatal accommodation in hospitals. Even in the existing circumstances, those areas with more hospital facilities appear to have a lower neonatal death-rate and stillbirth-rate associated with prematurity.

(b) *Care of the Premature Baby.*

Until such measures to reduce the incidence of premature birth have been adopted, this second method of treating the problem offers the best hope of success. To reduce the natal and neonatal mortality of these cases, every premature labour should preferably be delivered in a maternity hospital fully equipped to deal with the baby. There should not be a place for the treatment of premature labour in domiciliary practice. As an alternative, the babies could be transferred to a special hospital, irrespective of where they were born, in specially equipped ambulances, after the scheme adopted by Hess[11] in Chicago.

The lack of hospital facilities, particularly for this branch of paediatrics, is probably responsible for the high neonatal mortality-rates in areas such as South Wales and Northumberland and Durham. The medical problems of the care of the premature baby have been greatly clarified and improved, as the results quoted above have shown.

The reduction of premature birth, with its resultant stillbirth and neonatal mortality is a medical and an economic problem of outstanding importance. Its obstetric and paediatric associations are capable of remedy to a greater or lesser extent, but only as the result of widespread administrative measures on the lines indicated, the problem resolving itself largely, but by no means entirely, into an economic one.

In conclusion, I would like to echo McNeil's recommendation that in selected hospitals there should be radical investigations into the problem of prematurity by teams of obstetricians, paediatricians and pathologists, with a detailed analysis of home conditions, diet, and other domestic considerations.

SUMMARY.

One thousand cases of premature birth have been analysed.

The incidence varied from 27.2 per cent to 5.13 per cent for different types of cases.

The aetiology of the cases showed 372 cases without any cause, 319 cases induced

prematurely, and 309 cases with a definite cause, but not induced.

The overall results are given and discussed with other figures.

An attempt has been made to indicate in what direction any improvement of the problem may be expected.

Some recommendations for further investigation and solution of the problem have been given.

ACKNOWLEDGEMENTS.

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Some Curiosities of Mammalian Reproduction

Part I.—Mammals that have Triumphed over Anatomical Handicaps *

BY

FREDERIC WOOD JONES, M.B., D.Sc., F.R.S.

(A) CURIOSITIES OF EXTERNAL SEXUAL CHARACTERS.

ANIMALS THAT HAVE POPULARLY BEEN THOUGHT CAPABLE OF CHANGING THEIR SEX.

" As early as Aristotle it was a vulgar belief that the hyena changed its sex every year, or that each animal was both male and female. Aristotle denies this, but Oppian asserts it, as does also Aelian. Pliny accepts Aristotle's denial, but the belief remained throughout the Middle Ages. Hares were also believed to change their sex annually."
(*Ansell Robin*, p. 104).

THE sexual peculiarities of the hyena were given wide currency in medieval literature. The hare as a symbol of changing sex has become familiar by the allusions of Nashe in *Have with you to Saffron Walden*, Fletcher in *The Faithful Shepherdess*, Samuel Butler in *Hudibras*, and Isaak Walton in *The Compleat Angler*. Sir Thomas Browne devoted a whole chapter to the hare in *Pseudodoxia Epidemica*: but, although it has taken its place in country lore, the legend of the mole's change of sex seems to have failed to become a topic to which any attention has been given in literature.

(1) *THE SPOTTED HYENA THAT TRIUMPHS BY PHYSIOLOGICAL ADAPTABILITY.*

THE EXTERNAL SEXUAL CHARACTERS OF THE SPOTTED HYENA (*Crocuta crocuta*)

" Lyly asserts: ' Hiena, when she speaketh like a man, deviseth most mischiefe,' and Gosson, in *The Schoole of Abuse*, ' Hyena speaks like a friend, and devours like a foe.' Pliny says that this animal, by listening to the voices of men talking together, learns the name of one of them and calls him in a feigned human voice, which allures him to his death. He probably read this in Agatharchides, who records it sceptically of the *Crocottas*, which was perhaps only another name for the hyena. Aelian says the same, calling the animal *Corocotta*. Aristotle has stated that the hyena attracts dogs by imitating the sound of a man vomiting and Pliny and Aelian repeat this. Lodge perhaps refers to the mournful howl of the animal when he says: ' As the hyena when he mourns, so then most guileful,' but Ben Jonson attributes hypocritical tears to the hyena: ' Out, thou damned camelion harlot, now thine eyes vie tears with the hyena.' "
(*Ansell Robin*, p. 49).

It is evident that the hyena has been regarded with some suspicion, and considered as a deceptive sort of animal by men of many lands and in many periods. Added to the traditional belief in the deceitful nature of the animal, there has always been the suspicion that there was something not quite straightforward about its sex.

According to Morrison Watson, the first anatomist to recognize the very peculiar arrangement of the female sexual system of the spotted hyena was A. H. Garrod. Writing in 1877, Watson says that, " some time since," Garrod examined an animal that had died in the Zoological Society's Gardens in London. Apparently the arrangement that he found appeared so strange to him that he could not believe

*Lloyd Roberts Lecture delivered March 14th, 1944, Part I.

it to be normal. "The structure of these organs, however, struck him as so peculiar that he hesitated to publish an account of his dissection until such time as he should be able to verify his observations by the examination of a second specimen." This hesitation to publish was doubtless high testimony to Garrod's scientific caution, but it seems strange that, considering the wide currency of the hyena sex legends, Garrod did not trust his own first-hand observations that, in last resort, fell simply into line with Etienne Geoffroy's account, published as long ago as 1829, of the anatomy of the female mole. Even Watson felt the same doubt when he had completed the dissection of his specimen for he says: "Feeling uncertain on account of the very unusual condition of the female organs whether they were to be regarded as normal, I applied to Mr. Garrod for information. He at once, in the most generous manner, forwarded to me for comparison what remained of his own dissection and, in the note which accompanied it, showed that he had clearly recognized the peculiarities in question." Thus reassured, Watson published his observations, very beautifully illustrated by Dr. Alfred Young, his demonstrator of anatomy at Manchester University.

Eleven years after the appearance of Morrison Watson's paper in the Proceedings of the Zoological Society of London, Henry C. Chapman, of Jefferson Medical College, dissected a female spotted hyena that had died in the Zoological Gardens at Philadelphia. His published results confirmed in every detail the conclusions at which Watson had arrived. From the point of view of the anatomist the female sexual peculiarities of the hyena were firmly established, but as much still remained mysterious concerning the reproductive history, Harrison Matthews set out for East Africa in 1935 and examined over 100 animals killed around his camp on the Balbal Plains in Tanganyika Territory.

The facts concerning the sexual life of the spotted hyena are now well ascertained and it is quite clear that there is much justification for the ancient legends concerning the beast. All spotted hyenas are practically alike in outward sex and all look like males. Unlike the mole, the spotted hyena makes no anatomical readjustments during the breeding season and insemination and parturition take place by way of the genito-urinary channel opening at the tip of the female phallus.

Unfortunately, the embryonic stages of development have not so far been recorded: but there is little difficulty, when we have followed the phases in the mole, in reconstructing the stages by which the adult condition has almost certainly been attained. We may feel assurance in supposing that the inner genital folds, bordering the urethral groove on the phallus of both sexes, meet and fuse in the mid-line to enclose a complete phallic urethra in male and female alike (See Fig. 4). Into this phallic urethra there will open the two Müllerian ducts as they do in embryos of the mole up to the 27 mm. stage. But at this phase of development the embryos of the two animals almost certainly part company: for whereas in the mole the ducts lose their continuity with the urinary passages, in the hyena this continuity is retained. From the stage in which the ducts are present as two separate structures, development proceeds on the same lines in the two animals, for in both the ducts fuse together and form a common median utero-vaginal canal. But this utero-vaginal canal, which in the mole ends blindly as the Müllerian cell strands, in the hyena still opens as a patent canal into the urinary tract and so leads to a urogenital sinus that passes along the whole length of the phallus to open at the "urinary"

(urogenital) meatus at its tip. The female hyena has, therefore, perpetuated into the adult condition the phase present in the female mole embryo of the pre-27 mm. stage. From this phase there is no return and so it comes about that the only outlet for the female reproductive system is at the urogenital orifice at the tip of the clitoris: and this orifice in the sexually mature but non-parous female is no larger than is the urinary meatus of the male.

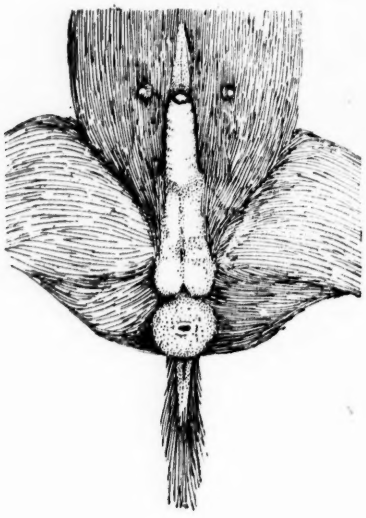

FIG. 1.

The external genitalia of a prepubertal female spotted hyena approaching the first oestrous. (After Harrison Matthews and the original specimens of Morrison Watson.)

The external genitalia of the adult female have been amply described and figured by both Morrison Watson and Harrison Matthews. The resemblance between male and female is very close. The phallus of the two sexes is almost identical and the likeness is increased by the presence of swellings in the female similar in appearance to the scrotal prominences in the male. The free portion of the phallus in the young female before puberty is some 5.0 cm. in length and 2.5 to 3.0 cm. in diameter at its base. It is therefore almost identical with the penis of the male which is from 4.0 to 6.4 cm. in length and 2.5 to 3.5 cm. in diameter at its base (See Figs. 1 and 2). The prepuce covers the glans. The glans itself is similar to that of the male and differs from it only in being slightly smaller. As in the male, the glans is provided with a well-marked fraenum preputii and the "urinary" meatus is similar in position, appearance and size to that in the male. It is a small, longitudinal slit only 2.0 to 3.0 mm. in length and is situated at the dorsal aspect of the tip of the glans. This little slit—2.5 mm. long—is the only opening by which the bladder and urethra, and the uterus and vagina, open to the surface of the body. Perhaps even more remarkable than this is the fact that the glans of the female is armed, like that of the male,

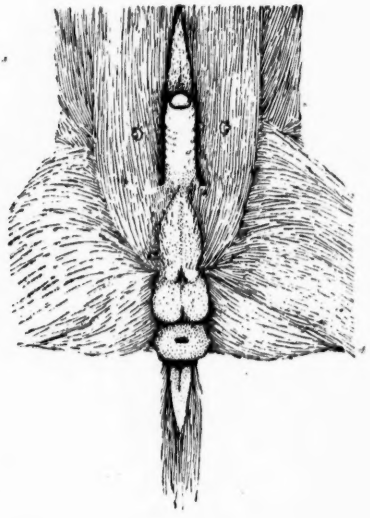

FIG. 2.

The external genitalia of an adult male spotted hyena. (After Harrison Matthews and the original specimens of Morrison Watson.)

with those little horny spines, so common and often so elaborate on the male copulatory organs of mammals of many Orders, that are best termed copulatory spurs or grapples. Harrison Matthews says of these female copulatory spurs that "they may be a trifle smaller than in the male," but evidently the disparity in size must be trivial for so careful an observer to have made no more definite a pronouncement.

Behind the base of the female phallus is a bare skin area, wrinkled as it is in the male, and on which there are two prominent swellings "closely resembling the scrotal pouches of the male." Although "they are indistinguishable from the condition found in those males in which the testes are not prominently descended," they are merely elevations marking subcutaneous pads of fibrous and fatty tissue and are obviously scrotal areas developed on the labio-scrotal folds. It is therefore clear that the differences between male and female genitalia are extremely insignificant and that the little slit only some 2 mm. in length, situated at the apex of the glans, is the sole orifice by which insemination and parturition can possibly take place (See Figs. 2 and 3).

Although there are some changes in the external genitalia of the female at the first breeding season, they are by no means extensive or dramatic. Nevertheless, they are curious manifestations of alterations that seem to be adopted as a sort of makeshift attempt to alleviate the condition. In the sexually mature female that has as yet to bear young, the prepuce becomes more lax and redundant so that the glans becomes more readily exposed. The fraenum of the glans hypertrophies and the "urinary" meatus becomes enlarged. When these processes are complete, the meatus of the female changes from being a mere slit some 2 mm. in length, situated somewhat dorsally on the tip of the glans, to a longitudinal opening about 1.5 cm. in length on the ventral aspect of the tip of the glans. The fraenum has, in fact, enlarged and then become cleft in the middle line so that the meatus is now bounded on either side by the two halves of the fraenum.

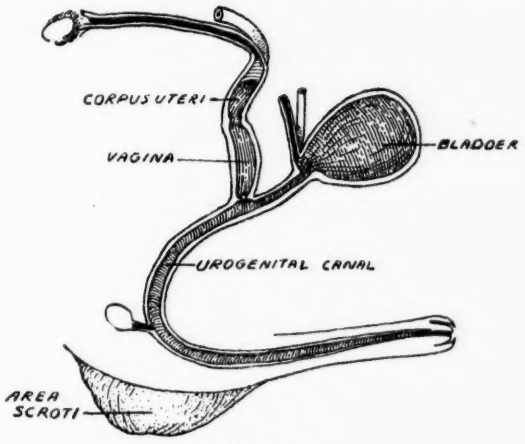

FIG. 3.

The internal genitalia of the female spotted hyena. Diagrammatic section founded on the work of Harrison Matthews and Morrison Watson.

The attempt that the spotted hyena makes to rectify the initial handicap of its masculine method of forming the female external genitalia, is a partial opening of the inner genital folds that met in the early embryonic stages to complete the tunnel of the phallic urinary canal. This attempted undoing of the embryonic closure affects only the urinary passage within the glans; it does not trespass on the urinary canal situated within the body of the phallus. It therefore improves matters only to the extent of converting a slit-like opening of 2 mm. into one of 15 mm. in length. This is the optimal condition arrived at before pairing and subsequent reproduction.

There is one other curious feature that adds strikingly to the outward similarity of the two sexes. In both male and female the nipples, surrounded by definite areolae, are situated on the abdominal wall alongside the phallus. In the sexually mature but non-parous female "the nipples are practically indistinguishable from the rudimentary nipples of the male, and are about 5 mm. in diameter and length."

The Internal Genitalia of the Female.

The description of the female genital passages as given in the accounts of Morrison Watson and Chapman left a loophole by which a comparatively simple explanation of the adult condition could be provided. Of the female passages Watson says: "The body of the uterus is found by the junction of the left and right horns. It measures 5 inches in length from the junction of the horns to the opening of the os uteri into the urogenital canal. That the whole of this is to be regarded as corpus uteri and not as constituting any part of the vagina is proved by the absence of any constriction in its interior which might correspond to an os uteri." Chapman held exactly the same view and states: "One of the most remarkable peculiarities of the female generative apparatus in *Hyaena crocuta*, to which we have hitherto only alluded, is the entire absence of a vagina, the uterus passing directly into the urogenital canal." If such were the true interpretation of the normal anatomical condition it was justifiable to claim that the real peculiarity of the female spotted hyena lay in the fact that it had failed to develop that portion of its genital tract that goes to the formation of the normal mammalian vagina. But Watson and Chapman were certainly wrong in thinking that the constriction that marks the junction of the female genital tract with the urinary canal represented the os uteri. The statement that the vagina is not present in the spotted hyena has become widely accepted, and Marshall (1922) in his standard work gives currency to it. But Matthews has definitely shown that the os uteri is not situated at the junction with the urogenital canal but is marked "externally by the presence of a slight thickening of the genital canal" at a point less than half way down the utero-vaginal canal. Within the canal its site is marked by a constriction of the lumen and by the typical change in character of the lining epithelium of the two morphological parts of the passage. The constriction at the junction of the genital and urinary passages, mistaken by Watson and Chapman for the os uteri, is the normal mammalian hymen. This hymen occupies its usual mammalian site and appears to serve the usual mammalian function of preventing the reflux of urine into the female genital passages.

The female spotted hyena, therefore, possesses a complete female genital tract, but this tract retains its original embryonic connexion with the urogenital sinus and the urogenital sinus, by reason of the peculiarities of the formation of the external genitalia of the female, has its only

opening via the little slit on the glans of the phallus (See Fig. 3).

Despite the smallness of the meatal orifice it is by this channel that the female is inseminated and the young are born. Concerning the method of coitus there have been the usual legendary tales and it seems a remarkable thing that, according to Matthews, the Masai natives who are thoroughly familiar with the animal are ignorant of the actual details and mistaken as to the postural relations. The act has been witnessed in the case of animals confined in Zoological Gardens (Grimpe, 1916; Schneider, 1926; Neuville, 1936). and the posture assumed differs only in minor details from that customary with pronograde mammals. Grimpe, possibly with unconscious humour, states that pairing takes place "amid loud laughter, which is characteristic of hyenas." The most remarkable fact, however, is that the female, after a period of gestation lasting 110 days, produces one or two young that are born in a remarkably advanced state. "They are large in size, have the eyes open, have erupted incisor and canine teeth and can walk, whereas, according to Grimpe, those of the striped hyena, in which there is nothing unusual about the female genitalia, are small, blind and completely toothless and helpless" (Harrison Matthews).

From the point of view of the mammalian taxonomist it is a disconcerting thing that within the *Family Hyaenidae* containing only three living species, all generally similar and all inhabiting the same geographical area, one species—the spotted hyena—should be so thoroughly eccentric in its sexual characters and the other two—the striped hyena and the brown hyena—should be perfectly normal in this respect.

Truly the spotted hyena deserves its legendary fame: but perhaps instead of regarding it as an emblem of deceitfulness it would be better to acclaim its resourcefulness in the successful triumph over physical handicaps.

(2) *THE EUROPEAN MOLE THAT SOLVES THE PROBLEM BY AN ANATOMICAL CHANGE BEFORE PREGNANCY.*

The External Sexual Characters of the Mole. (*Talpa europea*).

The mole is an animal that lives obscurely. It is not easy to observe in its natural state since the major portion of its life is spent underground. Nor may it be kept in captivity and studied with familiarity at close quarters.

It therefore happens that intimate acquaintance with the life history of the mole has been for the most part confined to professional mole-catchers, whose knowledge does not become incorporated into ordinary scientific literature, and to a few enthusiastic field naturalists who have made the animal the subject of special study. The first and most remarkable of these enthusiasts was Henri le Court, who resigned from his office in the French Court and, to escape the horrors of the Revolution, retired to the country and devoted the remainder of his life to a patient study of the mole. It was to le Court in his country retreat that the great Etienne Geoffroy St. Hilaire went for his knowledge and it was le Court's conclusions, given at second hand, that Geoffroy incorporated in his *Course de l'Histoire Naturelle des Mammifères*. Apparently le Court did not publish any account of his long investigations, though it is recorded of him that he trapped moles in such large numbers that during one period of 5 months he captured 6,000 in a comparatively small district. He had, however, a friend and pupil, Antoine Alexis Cadet de Vaux, and much of the knowledge gained by le Court is

embodied in the little book "*De la Taupe, de ses moeurs, de ses habitudes et des moyens de la detruir,*" published by de Vaux in Paris, in 1803. Most of the information given in natural history books that has any claim to accuracy has its ultimate source in this little book. Superstition and legendary tales of its blindness, of its incessant toil and of the perfection of geometrical design displayed in the construction of its burrows constituted almost the sole stock-in-trade of most writers on natural history. Towards the end of the 19th century more serious efforts were made to establish the truth about the habits of the mole; but it was not until 1902 when Lionel Adams, after devoting 4 years to a study of moles in the neighbourhood of Stafford, published his observations, that the age of legend passed into the era of real scientific knowledge.

Of all the legends concerning the mole, that which is most widely distributed and most commonly held by gamekeepers, mole-trappers and country folk generally, concerns the relative numbers of the two sexes. It is universally believed that the males are vastly more numerous than the females. This belief is the foundation of the other piece of information retailed in most works on natural history, that the males are extremely pugnacious and that the mating season is a period in which bloody battles and the killing off of the superfluous males produce a more equal distribution of the two sexes. When I was a boy I knew a mole-catcher who was well acquainted with this belief and he knew well that the majority of moles had every outward appearance of the male sex. But he did not believe in the reality of the mating season battles, nor did he think that the numbers of the seeming males were reduced by any other cause of death. If it were original with him or not I do not know, but he transferred the older traditions concerning the exotic hyena to the familiar mole, for he held firmly to the belief that the mole was capable of changing its sex. He did not claim that this interchange of sex could take place at random and in either direction but he had satisfied himself that all moles were apparently of the same sex during their first year, and only in their second season did they become truly males and females with external characters fully declaring their real sex. In 1912, when investigating the development of the external genitalia of the mammals, I examined a series of mole embryos. The peculiarities of the method of formation of the external sexual organs brought back the mole-catcher's theories to my mind and subsequent studies during the next 2 years made it clear that there was much to be said for his views; that Geoffroy had, in fact, known the truth and that Lionel Adams among the moderns had revealed some of the curious changes that punctuate the sexual life of this common but familiar animal. The facts are, briefly as follows. As the mole-catcher maintained, all moles are practicaly alike in outward sex and all look like males during their first year. It is only during the reproductive season in their second year that the females develop any outward characters distinctive of their sex.

The Embryonic Stages of Development of the External Genitalia.

The embryo at the stage at which it is 9 mm. long from vertex to caudal bend shows all the rudiments of the essential structures involved in the formation of the external genitalia. In embryos at this stage of development the cloaca is a wide orifice situated immediately in front of the root of the tail and from the anterior ventral margin of the cloaca the prominent genital tubercle projects. The tubercle is already

elongated and it is marked upon its cloacal aspect by a median urethral groove. The margins of the groove are slightly raised and constitute the inner genital folds (genital folds). These margins are faint and approximated to the mid-line towards the free tip of the phallus, but at its base they become widely separated and, passing round the cloacal margins, become lost within them. At the sides of the base of the genital tubercle are two prominent swellings which, at this stage, fade out about mid way in the length of the phallus and extend backwards to the lips of the cloaca. These swellings are the outer genital folds (labioscrotal folds). (See Fig. 4).

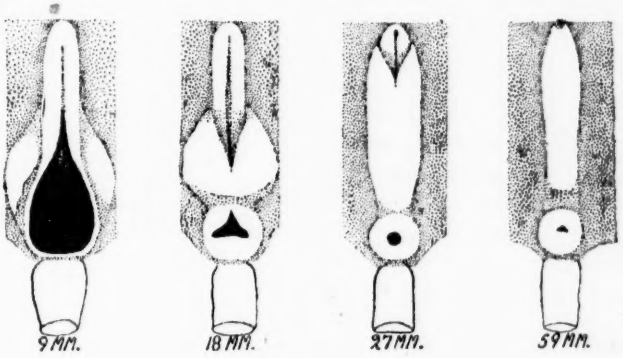

FIG. 4.

Developmental stages of the external genitalia of the mole. The condition is identical in the two sexes.

At a later stage, when the embryo is 18 mm. long, the genital tubercle has become conspicuously larger. It is unmistakably the intromittent organ and, as microscopical examination shows, it is alike in the two sexes. The phallic urethra has now been constituted as a complete canal by a closing of the urethral groove by the meeting of the inner genital folds at a median raphe. The striking feature of the changes produced from the 9 mm. stage is, however, the extensive development of the labioscrotal folds. These no longer remain as two lateral localized swellings, for they have fused in the mid line and have completely buried the base of the genital tubercle in front of the anterior margin of the cloaca. The genital tubercle with its completed urethral canal has now become ensheathed, over about half of its total length, by the overgrowing labioscrotal folds. The meeting of the labioscrotal folds at the base of the genital tubercle has cut off the tubercle and its enclosed urinary canal from the previously undivided cloacal orifice. This orifice now persists as the anus which, surrounded by the original raised margins of the cloaca derived from the labioscrotal folds, is triangular in shape. The apex of the triangle is at the original meeting place of the labioscrotal folds and this primary junctional area persists as a constriction between the base of the genital tubercle and the anal margin. About half the length of the phallus still remains unsheathed by the overgrowth of the labioscrotal folds and on this unsheathed portion the urethral raphe is clearly visible, the urinary canal, formed beneath the raphe, falling short of the extreme tip of the exposed phallus. When the embryo has attained the length

of 27 mm. the external genitalia are approaching their adult condition. The overgrowth of the labioscrotal folds has become so preponderant in the picture that almost the whole length of the genital tubercle and its enclosed urethra have become hidden beneath their invading margins. Only the tip of the phallus and the urinary orifice remain exposed at the extremity of the labioscrotal sheath. The orifice of the anus has now attained a more circular outline and its margins have become more distinctly marked off from the general area of the perineum. The original meeting place of the labioscrotal folds at the base of the genital tubercle has now formed a definite constriction between the body of the phallus in front and the raised anal margin behind.

When the embryo has reached term it is from 30 to 40 mm. in length, and now the genital tubercle has become completely ensheathed and hidden from view within a prepuce formed by the overgrowth of the labioscrotal folds. The anus is situated at the apex of a conical elevation of the skin surface and the original area of junction between the labioscrotal folds has become the flattened and relatively depressed area of the perineum. Upon this perineum there is naturally no median raphe, since the line of fusion of the inner genital folds is buried beneath the surface. The naked nestling shows exactly the same conditions, save that the phallus is considerably enlarged and the perineum, intervening between it and the conical elevation of the anus, has become more elongated.

The stages described are those that are common to the two sexes. There is no sexual differentiation to be detected in any phase of development of the external genitalia and the outward appearance of both males and females in the nestling stage is identical.

Judging from the phases which have taken place in embryonic development, it seems obvious that in the female, as well as in the male, the urogenital sinus must be carried forwards, by the closure of the inner genital folds, to the tip of the genital tubercle. This genital tubercle, with its urogenital canal, is then secondarily ensheathed within the overgrowing labioscrotal folds. It would thus appear, from external examination, that the processes by which the external genitalia are developed must have resulted in the functional end that both genital and urinary products find their only outlet, in both sexes, at the terminal orifice of the genital tubercle which becomes the penis and clitoris respectively in the two sexes. Herein the story of the mole evidently provides the clue to the mystery of the spotted hyena.

The Embryonic Stages of Development of the Internal Genitalia.

The correlation of the external appearances with the phases taking place in the internal reproductive system reveals several very curious happenings. The impossibility of determining the sex of embryos by external examination rendered this portion of the investigation particularly tedious, since serial sections of large numbers of embryos had to be prepared at random before sufficient material was available for determining the fate of the internal passages in the female. In the end complete serial sections of the whole extent of the ducts in female embryos of 27 mm. and 33 mm. were obtained.

In the female embryo of 27 mm. the arrangement of the female sex ducts (Müllerian ducts) is comparatively simple, for they run their normal course behind the urinary chamber of the entodermal cloaca and join separately into the dorsal wall of the urinary tract that, distal to their junction, is known as the urogenital sinus. As

the urinary passage passes from the bladder towards the urinary outlet at the tip of the phallus it describes a curved course. It descends from the bladder towards the hind end of the body and then turns up again, forming a 'U'-shaped bend, to join the urinary canal of the phallus. It is at the lowest part of this 'U'-shaped bend that the two Müllerian ducts join the urinary passage. From this point of junction onwards to the opening of the passage at the tip of the phallus the canal is therefore a common duct for both the urinary and reproductive systems. The opening of the separated Müllerian ducts into the urinary passage to form a terminal common canal —the urogenital sinus—is a primitive mammalian condition. It is the fact of the urogenital sinus tunnelling the whole length of the phallus, instead of having its own surface opening, that makes this stage of development in the mole (and in some other mammals) peculiar.

In the embryo 33 mm. in length a series of changes has taken place. The Müllerian ducts no longer open into the urogenital sinus, which thus again becomes a purely urinary canal. The two ducts have fused in the middle line in the lower part of their course to form a single median female passage, but this passage has no lower opening on the surface of the body. Below the common female passage the ducts separate again and, gradually losing their lumen, become mere blind cords of cells that pass backwards towards the skin surface of the perineum. These two "Müllerian strands" are separated from the urethral wall and may be traced as cell cords towards the base of the phallus (See Fig. 5). The phallus itself is covered by the ordinary many-layered skin of the original labio-scrotal folds, but upon either side of the base of the phallus, just where it joins the general skin surface of the perineum, the deeper layers of the skin dip inwards towards the deeper tissues of the body. These two ingrowths produce cell cords—the perineal strands—that pass inwards to become continuous with the extremities of the Müllerian strands. Both in the 27 mm. and 33 mm. embryos examined there was complete continuity between the perineal and Müllerian cell strands on only one side of the phallus, but since the ingrowth of perineal cells takes the form of a crescent around the root of the phallus this asymmetry is probably only a temporary phase.

At the 33 mm. stage the condition is therefore one in which the female ducts have met to form a common uterovaginal chamber but this chamber has no outlet, the old urogenital sinus openings having

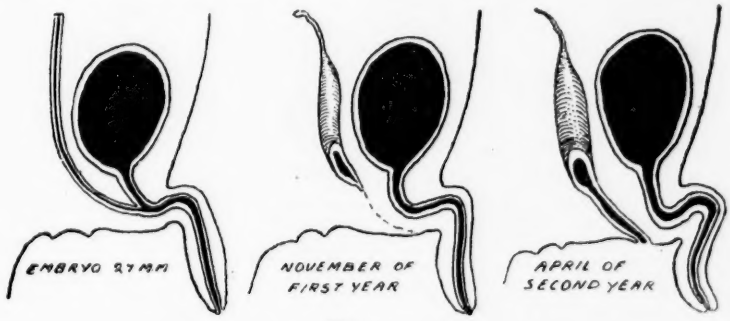

FIG. 5.
Diagrammatic sections through the pelvis of the female mole at different stages.

been lost. The walls of the common chamber are, however, in continuity with the skin of the surface of the perineum by the Müllerian cell strands and the perineal cell strands, which constitutes stream lines of tissue leading from the uterus to the surface of the body.

The next developmental phase is seen in the naked new-born nestling. In a female nestling 59 mm. in length the lower portion of the female genital tract has lost all trace of its bilateral origin, for the uterovaginal canal is a wide open passage far larger than the urinary canal. But the uterovaginal canal still has no opening, for the perineal strands, although having undergone further development, are still solid cellular ingrowths without any sort of lumen to constitute an external orifice for the reproductive system.

THE POSTNATAL STAGES OF DEVELOPMENT.

In most parts of England moles are born during the month of May. The young are naked at birth, and it is not until the 9th day that they change from being pink in colour to the dull lead hue that marks the advent of hair. At about the end of the first fortnight the actual hair appears. Postnatal growth is rapid; according to Adams the young double their length in the first 10 days of life; 3 weeks after birth they are three-quarters grown (Forrest), and by the later months of the year they resemble the adults of the previous year in all obvious characters. The only difference between moles in their first year and those in their second and subsequent years is, as Thomas Bell said, that "it is very difficult to know a virgin female mole from the male by mere external examination," whereas the sex of the female of the second year is easily recognized.

From among a series of moles captured in the November of their first year (when they are 6 months old) it is not difficult, after some experience, to pick out the females. But it is a very difficult matter to be certain of the sex of an isolated animal when comparison with other individuals is not possible. The sexual differences that may be detected when comparison of the two sexes is possible are confined to the phallus and the perineal area. The phallus of the female, though at first sight identical with the penis of the male, is, as a rule, slightly smaller when comparison is made with a male of the same age. The phallus of the male shows in variable degree a slight constriction at its base and so is somewhat delimited at its origin from the general perineal area. The phallus of the female on the other hand slopes more gently at its base and tends to merge, without delimitation, into the perineum. The other distinguishing feature, which was noted by Geoffroy, is that the distance from the base of the phallus to the anus tends to be less in the female than in the male. As a rule, therefore, the female has a shorter perineum than the male, but the distinction is not always very well marked.

It is not until the end of March in the following year that any obvious change takes place in the external genitalia of the female. Once these changes are initiated a complete transformation takes place with astonishing rapidity. As with many small mammals—and especially in the case of the insectivora—the onset of the sexual season is the time of a remarkable flare-up in the mole. The whole conduct of the animal changes and physical alterations in anatomical structures take place very rapidly. Both Lecaillon and Regaud are agreed that the changes in the male sexual gland are so dramatic that the testis actually increases 64 times in size during the month of March in the animal's second year of life. There is also an enormous increase in the size of the prostate glands.

The changes in the female are equally

striking. Towards the end of March the skin of the whole perineal area becomes markedly more pink in colour, the tissues are evidently considerably more vascular than they were at the beginning of the month. The phallus becomes deeply injected and is conspicuously red. The anal region shares in the added blood supply but does not attain to the striking redness displayed by the sexual area. The perineum itself has a cyanosed appearance and, suffused with a purple coloration in all specimens, becomes distinctly bluish in some. At the end of March the pigmentation of the perineum becomes more vivid, the whole area is enlarged and highly vascular and the blueness is accentuated around the posterior part of the base of the phallus. This intense pigmentation takes the form of a crescentic area embracing the base of the genital tubercle and reaching its maximum at two points situated upon either side of the phallus. These points of intense pigmentation correspond to the areas beneath which the perineal strands have penetrated the tissues towards the Müllerian cell strands. At these two points the actual perforation of the perineal skin makes its first appearance and dissolution of tissues spreads along the cresentic line of pigment until finally, generally in the first week in April in Surrey, a transverse orifice is conspicuous on the hyperaemic skin of the perineum just behind the base of the phallus. This newly established vulval orifice is a mere break in the tissue continuity (See Fig. 6). Its margins naturally do not show any appearance of lateral folds or other structures such as are present at the vulval orifices of more normal female mammals whose external genitalia are formed on more familiar lines. Towards the end of April the colour fades from the perineum but the vulval orifice remains widely patent and, usually during the month of May, parturition occurs. After parturition, retrogressive changes take place rapidly. The vulval orifice becomes increasingly less conspicuous and connexion between it and the uterovaginal canal becomes obliterated. There is some variability in the degree to which the actual vulva is involuted. Some females examined in late summer show nothing more than a wrinkled surface at the anterior margin of the perineum to mark where the orifice has been obliterated. Some show minute areas

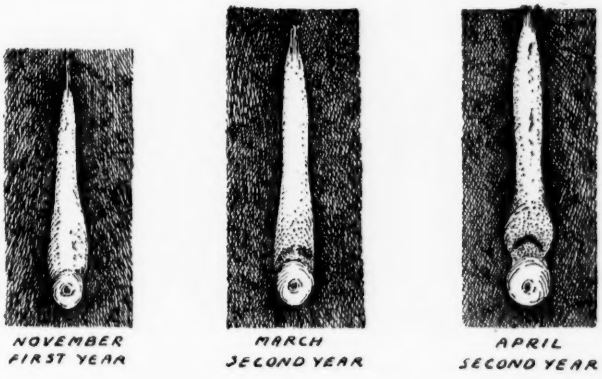

FIG. 6.
Changes in the external genitalia of the female mole.

of pigmentation along the line of closure of the vulva. In others a definite, puckered and somewhat irregular scar

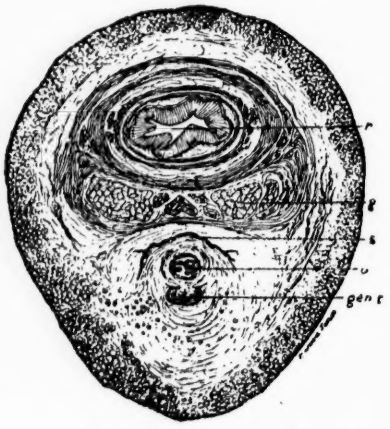

FIG. 7.

Section of the pelvis of a female mole during November of its first year.
R = rectum; G = Sex gland; S = Strand of solid tissue uniting the female genital passages to the skin at the base of the genital tubercle. U = Urethra; Gen. t. = Genital tubercle.

marks the vulval site. At times irregularities and pockets are present in this scarred area and, in one November female, a probe could be passed inwards from the skin surface for some distance; but this pocket made no connexion with the utero-vaginal canal.

The internal genitalia of the female undergo an even more striking development during the end of March and beginning of April. All parts of the female genital tract become highly vascularized and show a very rapid increase in size. (See Figs. 7 and 8). The lower part of the uterovaginal canal ceases to be a mere solid mass terminating in solid Müllerian cell strands, for the whole of the tract becomes a wide-open canal by a process of desquamation of the central cells of the previously solid cell mass. The peripheral cells of the Müllerian and perineal cell strands become the epithelial lining of the newly formed passages and in this way a complete epithelially-lined vulvovaginal canal is formed. With this completion of the female genital tract an enormous growth of the anal sex gland takes place and the whole topographical anatomy of the pelvic region undergoes a profound change. After parturition, retrogressive processes are rapid. The lower portion of the utero-vaginal canal becomes closed again by the approximation of its anterior and posterior walls; it lumen diminishes and cell proliferation again renders it imperforate. Like the closure of the vulval orifice on the surface of the perineum, the occlusion of the lower part of the utero-vaginal canal may show various irregularities. The epithelial occlusion is not always uniformly carried out but, though irregular portions

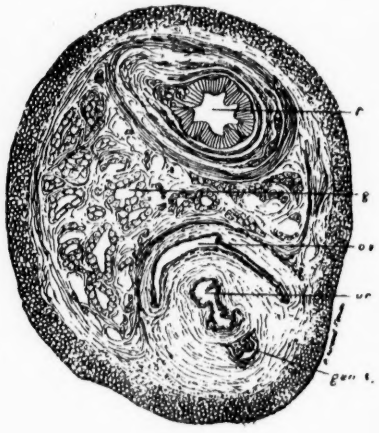

FIG. 8.

Section of the pelvis of a female mole during the April of its second year.
R = Rectum; G = Sex gland; O.V. = Opened vaginal orifice (see S in previous figure). U.R. = Urethra; Gen. t. = Genital tubercle.

of the lumen of the uterovaginal canal and irregular pockets of the vulval orifices may persist in winter females, these, as a rule,

do not effect any junction with each other.

It is obvious that, if female moles undergo a reproductive period in their third year, the whole process must be repeated during the sexual season.

As is usual with animals showing strange or puzzling features in their external genitalia, legends have grown up about the methods by which pairing takes place. These legends mostly take their place in folk-lore, and such are the traditions woven around the sexual habits of elephants and camels. In the case of the mole the current myth found its origin, or at any rate its expression, in a work written for the scientific zoologist and not for the common people. It was Thomas Bell who, writing of the perineum of the virgin mole, said: "As this covering is so tense the utility of the little bone at the extremity of the penis in the male is very obvious, and its pointed and tapering form is at once accounted for: it is clearly intended to perforate this tense covering of the vagina."

There are many curiosities of mammalian anatomy concerned in the form and development of the baculum or penile bone, but there are few curiosities of reasoning upon structure and function more remarkable than this declaration of Thomas Bell's.

The mole is not unique among mammals in that the phallus of the female approximates the degree of development present in the male. Some of the animals included in the Order *Primates* exhibit this condition. In one of the lemurs (*Hemigalago*) a baculum or penile bone may even be present in the clitoris and the enlargement of the female phallus is conspicuous in the spider monkeys (*Ateleus*) and in one of the gibbons (*Hylobates concolor*). These highly developed female phalluses are generally marked by a pronounced urethral groove: but the urethra opens in the normal way at the base of the phallus. Nor is the mole unique in having a female phallus comparable with that of the male in size and also tunnelled in the whole of its length by the urinary canal. This is the condition that is characteristic of the lorisine lemurs as distinct from the lemurine or true lemurs. It is also present in certain rodents (*Capromys, Arvicola*, etc.), and in some other insectivores (*Sorex*). In all these instances the adult peculiarity is brought about by the overgrowing female genital folds in the very early stages of embryonic development. Again, the mole is not alone among mammals in that it shows a postnatal opening up of the female genital passages, for the same condition prevails in certain rodents in which the immature female vagina is imperforate. Some of the shrews and possibly other small and inconspicuous insectivores exhibit the same peculiarity.

But the mole is an outstanding example of an animal that went astray in adopting the same method of formation of the external genitalia in both male and female. Having applied the masculine processes of development to the female at a very early embryonic period, it is left with a masculine urinary passage which also furnishes the only outlet of the female reproductive system. The mole, however, rises superior to this initial developmental handicap by a very ingenious method, for it develops an open female genital passage during its first breeding season. The opening is brought about by a process that is not unlike that seen in the development of these passages in the embryonic stages of other mammals. That they become closed again, once the young have been born, is again a thing not unparalled in the mammalia, for similar processes are rehearsed in the curious story of the development of the median vagina of the marsupials. We may look upon the mole as an animal that has triumphed over an initial anatomical handicap by resorting in an emergency to

peculiar anatomical makeshifts and here it differs from the spotted hyena, for though this animal's physiological solution of the problem may appear even more wonderful, it lacks the structural resourcefulness that is displayed by the mole.

The spotted hyena and the mole have the distinction that although the external genitalia of the female are not developed along the usual mammalian lines, their internal genitalia are of the typical higher mammalian form. The problem of the handicap is solved by the hyena without any major anatomical readjustments: but the mole resorts to an expedient by which insemination and the birth of the young may be effected by a new and temporary channel.

There is, however, still another group of mammals that suffers from an initial handicap in the method of formation of the female reproductive tract and it is here the internal and not the external parts of the system that stand in need of anatomical readjustment.

(B) CURIOSITIES OF INTERNAL SEXUAL CHARACTERS.

The Marsupials that wait until they are Pregnant and then Effect Anatomical Changes on the Emergency.

Of the opossum from New Holland John Hunter wrote: "There is something in the mode of propagation in this animal that deviates from all others; and although known in some degree to be extraordinary, yet it has never been attempted, where opportunity afforded, to complete the investigation." He was forced to admit that "although I have a great many facts respecting them, yet I am not certain that I am possessed of sufficient information to complete the system of propagation in this class."

Even to-day in Australia, after an interval of 2 centuries, the average man who is regarded by his fellows as an authority on the marsupials, because in his time he has slaughtered great numbers of them for their pelts, is in no better case than was John Hunter. Despite the scientific advances made in the interval he still is not "possessed of sufficient information" to permit him to understand the business: but he differs from John Hunter in that he fancies he understands it and so claims that he is entitled to the last word on the subject.

And in truth the propagation of these animals is a very strange affair that has only been told as a connected story during the last half century. Odd chapters had been written at intervals. Everard Home, so long ago as 1785, had learned much of the truth from Hunter's notes and dissections and from the examination of specimens sent to Hunter from New South Wales too late for the master himself to solve the problem. Richard Owen added a further chapter and Lister and Fletcher, in more recent times, had come within measurable distance of writing the final pages. But it was not until 1899 that J. P. Hill, working in Sydney, filled in the gaps and let us read the whole strange story in its continuity.

With the marsupials there is no question of failure to distinguish the two sexes by the characters of the external genitalia. External sex characters are particularly well marked in the whole assemblage of the Didelphidae. It is with the internal genitalia and the internal genitalia of the female alone that the anatomical pecularities of the phylum are displayed.

There have been many definitions of just what we mean by the term marsupial animal. The first and most popular—that they are animals possessing a marsupial pouch—we will dismiss at once, for the most typical primitive marsupials have no

pouch whatever. The pouch is a marsupial development: it is in no way a marsupial hallmark. The second—that they are non-

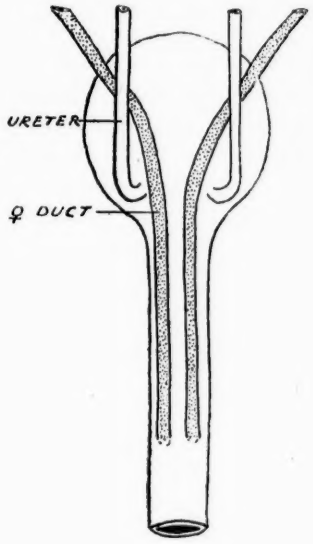

FIG. 9.
Diagram of the early stages of the female genital ducts of a higher mammal.

placental mammals—is completely devoid of truth. Marsupials show certain peculiarities in their skeletons and in their brains, but even these are not always sufficiently well marked in all of them to sunder the whole group from those higher mammals that vary in similar directions. It cannot be too strongly insisted that the feature that distinguishes all marsupials from all other mammals is the fact that in them the ureters pass between the female genital ducts, whereas in all other mammals they pass lateral to them. It is this initial fact in early embryological development that determines all the other peculiarities and makeshifts of the female internal genitalia and accounts for the whole strange sequence of events involved in the process of parturition.

In all the higher mammals the ureteric buds grow out from the primary excretory ducts of the embryo so that they pass to the developing kidneys on a course that is lateral to the Müllerian or female genital ducts. It may even be said that there is a critical stage in the development of the ureteric buds of the higher mammals in which it is touch and go with them. They start to grow backwards towards the female ducts and, for a time, it appears uncertain if they are destined to pass to the medial or the lateral side of the ducts. In the end they pass to the lateral side and the female genital ducts are left in the middle line of the body, free to unite with each other as they lie closely approximated side by side (See Fig. 9).

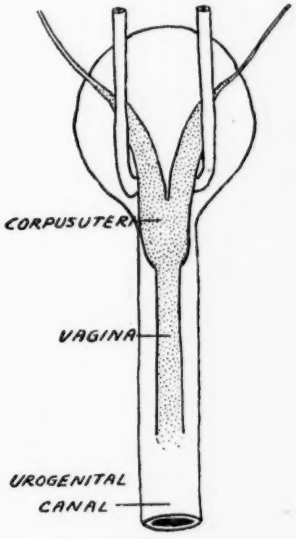

FIG. 10.
Later stage of the female genital ducts of a higher mammal. The ducts have fused in the midline to form a corpus uteri and the single median vagina is developed.

In the typical higher mammals the female genital ducts so approximated remain separated as the Falloppian tubes in their

most forward portions and then, over that part contained in the "genital cord," unite and fuse, forming a corpus uteri leading

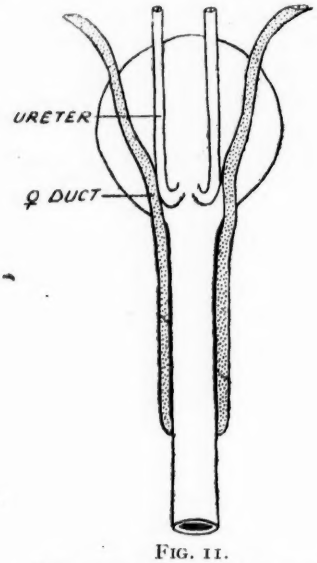

FIG. 11.
Diagram of the early stages of the female genital ducts of a marsupial. The genital ducts are separated by the ureters.

into a vaginal canal and so to the urogenital sinus and the exterior (See Fig. 10). There is no difficulty in forming a median uterus and vagina when the ureters and Müllerian ducts are arranged as they are in the higher mammals. But with the marsupials the case is very different. The ureters separate the female genital tubes and so make it impossible for them to unite in the middle line to form a single median passage (See Fig. 11). The whole of the female genital tract of the marsupial is therefore double and consists of two entirely separate halves. It was for this reason that De Blainville in 1816 gave the name Didelphia to the whole phylum and such a name, unlike marsupialia or metatheria, the commonly employed synonyms, has a real scientific taxonomic basis. The females of the primitive marsupials possess two separate uteri, two separate vaginae and two separate vaginal orifices in addition to the two usual separated Falloppian tubes (See Fig. 12). The two separated lateral vaginae open quite independently into the urogenital sinus and so to the surface of the body at the cloacal orifice. In harmony with this anatomical arrangement the penis of the male is bifid at its distil extremity. In the smaller marsupials the penis bears a very striking superficial resemblance to the forked tongue of a snake. Insemination is effected by the passage of the separated distal prolongations of the male urethra into both of the lateral vaginae of the female. Fertilization is effected high up in the female passages and then the dilemma, created by the dual nature of the

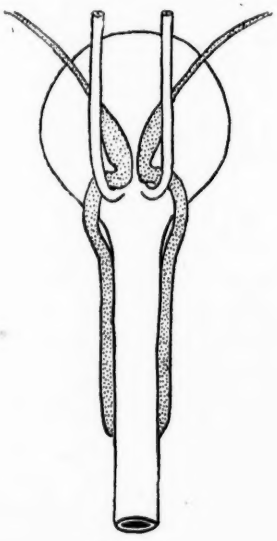

FIG. 12.
The female genital ducts of a marsupial at the stage in which they bend inwards over the ureters.

female reproductive tract, has to be faced. How are the young to be born? Will the two slender lateral vaginae, competent as

oviducts to pass ova to the exterior, suffice for the passage of living embryos to the outside world?

It is perhaps best to tell the story of the solution of the problem as a composite, without reference to the individual peculiarities seen in different species. In general, the first phase takes place before the advent of pregnancy in the higher

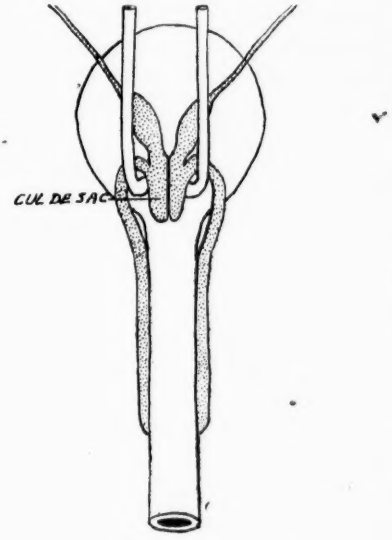

FIG. 13.
The female genital ducts of a marsupial at the stage in which the vaginal cul de sacs are developed between the ureters.

members of the group. The portions of the female genital ducts that lie cephalic to the point where the ureters enter the bladder begin to sag inwards towards the middle line. They do this by falling inwards over the two bars created by the loops of the entering ureters as they pass forwards to the bladder wall. At the point where the two tubes sag inwards over the ureters they become somewhat dilated so that the inwardly sagging parts are marked as two dependent bulges of the tubes. The actual part of the female genital tract that falls inwards across the ureteric bar is that which is situated immediately behind the segment specialized to become the uterine portion (See Fig. 12). The sagging portions of the two tubes that have fallen over the ureteric bars nearly meet each other in the middle line and the meeting is made the nearer by the dilatation of the tubes at this point. It thus comes about that two little bags, termed vaginal cul de sacs, are present as medial inbendings of the two lateral vaginae between the two ureters at their junction with the posterior bladder wall (See Fig. 13).

When the animal becomes pregnant the embryos pass into the separate uterine portions of the female tract and establish their short-lived placental connexions with the uterine tissues. From the two uteri the embryos have a natural and simple passage to the vaginal cul de sacs. But the fact of taking this route is, in itself, almost a prohibition to their passing into the distal portions of the lateral vaginae, even did the size of these canals readily permit of their taking this course. The embryos have passed into blind-end dilatations of the female passages. In the next phase the two vaginal cul de sacs, which have been considerably dilated by the bulk of the enclosed embryos, become approximated in the middle line and the septum that separates their two cavities breaks down. There is thus formed a single median pouch, derived from both the lateral vaginae, situated between and behind the entering ureters, in which the developing embryos are, for a time, retained. But the problem of the birth route still remains unsolved. The dilemma now consists in the fact that, though there is a median brood chamber, there is no median passage distal to it and the young still have no obvious outlet to the outer world. The solution of the problem is a dramatic one. By tissue rupture and with the extravasation of

blood, a passage is formed from the most dependent point of the median cul de sac to the urogenital sinus and the cloaca

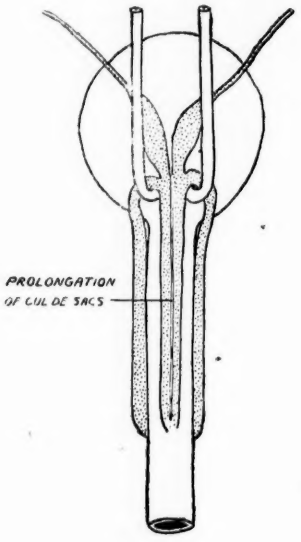

FIG. 14.

The female genital ducts of a marsupial at the stage in which the cul de sacs have become prolonged towards the urogenital sinus.

(See Figs. 14 and 15). Through this ruptured passage the young are born. Their umbilical cords are left in the passage through which they have passed, and when the rupture is repaired (as it is in the more primitive marsupials) these embryonic structures are incorporated into the scar tissue that occupies the site of the temporary birth canal.

This is the story of parturition in the more primitive marsupials. The new median passage is made on the emergency in order to permit the birth of the embryos through a rupture of all the tissues that intervene between their brood chamber and the outer world. The passage itself is no more than a lacerated rent in the tissues. As such it has no epithelial lining, no boundaries, no limiting wall and no membranous sheath. The passage is simply constituted by the torn tissues and the blood clot extravasated in their rupture. It is formed as a wound and as a wound it is healed. So quickly is this temporary channel repaired in the more primitive marsupials, that, in *Dasyurus*, the whole rent in the maternal tissue is completely healed and all the extravasated blood clot is absorbed by the second day after parturition (Hill). At every subsequent pregnancy the process is repeated. The embryos distend the cul de sacs, the ruptured tissues permit their escape to the cloaca and the outer world; and the healing process of the maternal rent is rapidly completed.

But, though this is the story of the progress of the phases of pregnancy and parturition in the more primitive members of the marsupial phylum, it is not the whole

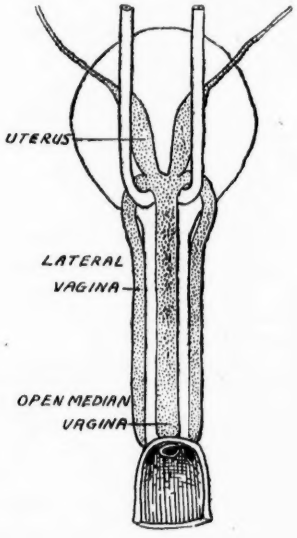

FIG. 15.

The final stage of the female ducts of a marsupial. The median vagina is completed and is open to the urogenital sinus and cloaca.

story when all the members of the phylum, from the most primitive to the most specialized, are passed in review. The first stage of phylogenetic advance is made in the early development of the two vaginal cul de sacs long in advance of the advent of the embryos. In some of the arboreal phytophagous forms (such as *Trichosurus*) these dilatations are already present in the female embryo when it is only 22 mm. in length. The vaginal cul de sacs have now become a definite birthright as a part of the individual's heritage. The cul de sacs in the adults of such forms are separated from each other only by a very thin partition. This partition breaks down early in pregnancy and once it has broken down it never heals up again. The single median brood chamber becomes a permanency after the animal has once been pregnant. The torn area by which the two originally separate chambers communicate becomes covered with epithelium and, in the parous female, only a slight ridge in the middle line of the chamber marks the original site of the septum. But even in these forms, although the median undivided diverticulum becomes a permanent anatomical feature, there still remains the necessity to make a temporary median vagina at the next parturition.

The more specialized saltatorial herbivorous marsupials made a further advance on this stage. The female pregnant for the first time rehearses all the stages of cul de sac formation and the development of the median birth passage. But when pregnancy terminates with the birth of the young, the healing of the median rent is delayed. During the interval, epithelium invades the surface of the median passage and prohibits the union of its walls. The result is that a permanently open canal persists, lined with epithelium and communicating on the one hand with the distal extremity of the median cul de sac and on the other with the cloaca. A permanent median vagina, in addition to the two original lateral vaginae, is therefore a normal anatomical feature of the females of certain of the kangaroos once they have born young.

The next stage is attained by certain other members of the *Macropodidae*. In some species it seems quite certain that the virgin female possesses a true median cul de sac prolonged as a true median vagina which is no mere tissue cleft but is an open tube with properly organized muscular walls and with a complete epithelial lining. This median vagina, which pre-exists impregnation and parturition, is no inconsiderable rudiment for, in the ordinary kangaroos, it is a tube nearly 3 inches long, having a bore of slightly under $\frac{1}{2}$ an inch. Obviously in this phylogenetic story, more and more has become incorporated into the birthright of the female marsupial and each step gained in heritage would seem to be a recapitulation of what was achieved with great adventure in the adult stages of the more primitive members. The median brood chamber has been made; the median vagina is perfected, provided with a muscular wall and lined by epithelium; all that the virgin female of most of the kangaroos lacks is the opening of the median vagina into the urogenital sinus.

Even this last step in the completion of an entirely replanned internal reproductive system is attained by certain of the wallabies. Brass (1880) reported a young virgin female *Wallabia rufogrisea bennetti* in which the median vagina was open to the urogenital sinus at its lower end and Lister and Fletcher (1881) found the same condition in a young virgin female *Wallabia bicolor* that lived its short life of 42 days under observation in the London Zoological Gardens.

The whole of the remodelled internal reproductive system, begot in an emer-

gency and rehearsed at every pregnancy by the more primitive members of the phylum, has now become incorporated into the embryological birthright of some of the more specialized members.

There is no doubt that the spotted hyena must claim our real admiration. This unprepossessing animal, faced by an almost ridiculous structural handicap, has succeeded, despite seemingly insuperable obstacles, in achieving its end without resorting to anatomical makeshifts. In legend and in proverb man has shown some contempt for the hyena, but perhaps when the whole story is told, it may be admitted that the animal has justification for its proverbial indulgence in derisive laughter.

The mole may be regarded with esteem as an animal that, though perhaps lacking the ingenious resourcefulness of the hyena in making shift with a very unpromising anatomical arrangement, has nevertheless met an apparently impossible situation by rapid but temporary alteration of structure. Satisfactory though the mole's solution of its difficulty is for the individual, it is one that has to be faced anew by every female at every breeding season. Nothing is gained as an anatomical permanency in the phylum of the moles, ancient though it is. It may be that in the case of the mole the reproductive life of the female is a short one and so the repetition of the process lacks that frequency in individual experience that is present in the marsupials.

But to the marsupials, as a phylum, must be given the credit for achievement. Here something permanent has been gained, for there is incorporated into the heritage of more specialized members the hard-won triumphs of the individuals of the more primitive types. For those interested in the question of the attainment of functional characters in embryological development in advance of the advent of the functions they subserve, the marsupials would seem to have an important message.

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CRITICAL REVIEW

The Aetiology of the Toxaemias of Late Pregnancy

BY

FRANCIS J. BROWNE, M.D., D.Sc., F.R.C.S., F.R.C.O.G.

Professor of Obstetrics and Gynaecology, University of London; Director of the Obstetric Unit, University College Hospital, London.

INTRODUCTION.

1. RÔLE OF THE INTERNAL SECRETORY GLANDS.
   - The Pituitary Gland.
   - The Suprarenal Glands.
   - The Anterior Pituitary-like Hormone.
2. DIETETIC FACTORS.
   - General Considerations.
   - Clinical Experiments: The Toronto Experiment. Peoples' League of Health Experiment.
3. PLACENTAL TOXIN THEORIES.
   - Placental Infarction (Young); (Bartholomew *et al.*).
   - Crush Syndrome.
   - Placental Ischaemia (Page).
4. THE PRESSURE THEORY.
5. PYELITIS AND TOXAEMIA.
6. ALLERGY.
7. THE RÔLE OF INFECTION.
8. CHEMICAL POISONS.
   - Guanidine.
   - Histamine.
   - Tyramine.
9. CONSTITUTIONAL PREDISPOSITION TO ECLAMPSIA.
10. THE RHESUS FACTOR IN TOXAEMIA.
11. THE KIDNEY IN TOXAEMIA.
    - Histological Changes.
    - Renal Function.
12. OEDEMA.
    - General Considerations.
    - Genesis of Oedema.
13. HYPERTENSION.
14. ALBUMINURIA.

IN this review it is proposed to deal only with pre-eclamptic toxaemia and eclampsia and chiefly with work done since 1930. For work before that time the reviews of Comyns Berkeley,[1] Eardley Holland,[2] and H. J. Stander[3] may be consulted. Investigations during the last 15 years have been concerned chiefly with:

(1) The possible *rôle* in aetiology of the internal secretory organs, especially the pituitary.

(2) The relation to aetiology of defects in diet.

(3) Application to the problem of the newer knowledge of renal physiology and pathology.

THE RÔLE OF THE INTERNAL SECRETORY GLANDS.

The Pituitary Gland. Anselmino, Hoffmann and Kennedy[4] using rabbits in their experiments, claimed that hyperfunction of the posterior pituitary gland was the

cause of water retention and oedema, capillary spasm, rise of blood-pressure and toxic albuminuria. They demonstrated the presence in excess of antidiuretic and pressor substances in ultra filtrates of the plasma in patients with toxic albuminuria of pregnancy or eclampsia, and the filtrate had chemical and physical properties identical with those of the internal secretions of the posterior pituitary gland. Twenty-five patients were investigated and antidiuretic principle was found in all in whom oedema was present. The pressor principle was recognized in all in whom blood-pressure exceeded 180 mm. Hg. Cushing[5, 180] described an infiltration of the posterior pituitary by basophile cells from the anterior lobe and pars intermedia in hypertension and eclampsia and stated his belief that it was the cause of these disorders. Further work however has not confirmed Cushing's claim and Biggart[6] reported, after examining sections of over 1,000 human hypophyses, including those of 8 eclamptics, that marked basophilic infiltration may be found in absence of either hypertension or eclampsia and that it does not seem to be more common in these conditions than in control glands of similar age periods.

Hoffmann, Anselmino and Kennedy's work has been repeated by many investigators who, using their methods, have tried to confirm their results. The results of these investigators have, taken as a whole, been decidedly unfavourable to their claim. Thus Hurwitz and Bullock[7] concluded that neither blood-pressure raising nor antidiuretic substance was found in the blood of 14 patients classified as pre-eclamptic toxaemia, eclampsia, and chronic nephritic toxaemia. Levitt[8] examined the blood of eclamptic patients for antidiuretic substance and concluded that there was a slight inhibition of water diuresis without altering the concentration of urinary chlorides. "If the blood of patients with eclampsia and related disturbances *does* contain an increased amount of the hormone from the posterior pituitary our present methods are unable to detect it." "For the present there is no good evidence that hyperfunction of the posterior lobe of the hypophysis is an important factor in eclampsia." Byrom and Wilson,[9] using rats, as they consider rabbits unsatisfactory for this particular work, and a method capable of detecting the antidiuretic hormone in a dilution of 0.002 I.U. per c.c. failed to reveal its presence. De Wesselow and Griffiths[10] examined blood of patients with essential and malignant hypertension and of 2 patients with pre-eclamptic toxaemia both with blood-pressures over 180 mm. Hg. and found "no evidence at all of the presence of a pressor body" in any. Irvine H. Page[11] failed to find any evidence that the amount of pressor substance was increased in the blood or spinal fluid of patients with hypertension of varied pathogenesis (nephritic hypertension, essential or malignant hypertension, eclampsia and pituitary basophilia). Theobald[12] concluded that the blood of eclamptic patients does show antidiuretic activity, but as the principle passes through a membrane known to be impermeable to infundin it is evidently not identical with the antidiuretic fraction obtained from the posterior pituitary gland. Apparently he did not carry out any experiments on the pressor principle as he thought it impossible it could raise blood-pressure to a high level. "There is," he says, "no experimental evidence to justify the assumption that the posterior pituitary pressor substance could elevate the systolic blood-pressure from the normal to over 180 mm. and maintain it at that level indefinitely, while all the available evidence goes to show that no marked rise of blood-pressure can be caused by posterior pituitary extract." Teel and

Reid[13] found that concentrates prepared from the *urine* of patients with pre-eclamptic toxaemia and eclampsia with oedema exerted a marked antidiuretic effect on water diuresis in rats. Similarly prepared extracts from the urine of normal pregnant women in the last 3 months of pregnancy exerted little or no antidiuretic effect. But if normal pregnant women were dehydrated by withholding water the urine then contained amounts of antidiuretic substance comparable with those found in pre-eclamptic and eclamptic patients. This antidiuretic principle in the urine resembles pituitrin and Teel and Reid[13] consider that its presence "offers an immediate mechanism for the water retention of pre-eclamptic toxaemia and eclampsia." Their results were confirmed by Krieger and Kilvington.[14] Melville[182] concluded that "the *data* obtained from examination of the blood of normal pregnant women and several cases of early toxaemia did not indicate any causal relationship between the presence of antidiuretic substances in the blood and the early symptoms (hypertension, oedema, albuminuria) of the toxaemias of pregnancy."

It thus appears that while the presence of a pressor substance in excess has not been confirmed by any of these workers, there is a difference of opinion about the antidiuretic substance, but that the only 2 workers who find an antidiuretic substance find it not in the serum but in the urine.

It appears, however, that even though an antidiuretic substance were present in excess it would not explain the often massive and rapidly occurring oedema of eclampsia. It is a matter of frequent observation that a patient may have anuria for several days without any oedema whatever. Myers[15] reported a case of total anuria lasting 30 days due to obstruction of both ureters by a cancerous growth. There was not any oedema except of the right side of the vulva and a moderate oedema of the right leg (evidently due to compression of large veins by the growth). When first seen by Myers 15 days after the onset of anuria he found a rather thin woman, definitely anaemic, with slight orbital padding and moderate swelling of the right leg only. Barry, Shafton and Ivy[16] reported that oedema does not occur in bilaterally nephrectomized dogs until water with excess of sodium chloride is supplied; neither is there any increase in weight. Water alone without salt did not cause oedema. This absence of oedema in anuria is what one would expect as the mode of action of antidiuretic substance in man is by acceleration of the reabsorption of water. Finally with regard to the pressor substance it is relevant to note that E. W. Page[17] found that if 400 c.c. of blood were rapidly transferred from patients with eclampsia or severe pre-eclamptic toxaemia to normal pregnant women the recipient did not show any rise of blood-pressure or interference with diuresis. Byrom[18] considers that the negative results quoted above do not necessarily exclude over-secretion of vasopressin for "the methods available for detecting it involve considerable dilution of the suspect fluid by the tissue fluids of the test animal." By injecting vasopressin into rats he was able to produce lesions closely resembling those of eclampsia including a rise of blood-pressure of 50 mm. Hg. or more. There was delayed excretion of water, albuminuria, coma and death. In the kidneys there was degeneration of the convoluted tubules, and cortical necrosis and in the liver focal necrosis (not histologically like that of eclampsia). He believed the lesion to be due to arterial spasm. He also found that the sensitivity of the rat could be increased 10 times by preliminary treatment

with oestrogens, and that in unspayed rats the sensitization could equally well be produced by gonodatrophic hormones.

These results are interpreted as supporting the view that the lesions of eclampsia and pre-eclamptic toxaemia are expressions of vascular spasm but he rejects the hypothesis that such spasm in eclampsia is due to over-secretion of vasopressin because the equivalent dose necessary in the human would be 250 to 800 units. "It is hardly credible that the natural hormone could reach such levels and it follows that, unless vasopressin is secreted by some other tissue in pregnancy, eclampsia cannot be wholly and may not be partly due to over-secretion of vasopressin. If the hypothesis of vascular spasm is accepted then either some unknown pressor agent is concerned or, alternatively, the vessels must become in some way hypersensitive." Addis[19] regards angiospasm as the common pathogenic factor underlying all the varying expressions of eclampsia. In the brain it results in hypertensive encephalopathy, in the kidney albuminuria and oliguria, in the liver in periportal necrosis. In the subcutaneous tissues it causes anasarca and in the skin pallor. He does not venture any opinion as to the cause of the angiospasm but it is not in his opinion due to obstruction in the renal circulation.

The Suprarenal Glands. Two functions of the adrenal gland are pre-eminent. First, regulation of mineral metabolism (especially that of sodium and potassium) and water balance, leading to retention of sodium and excretion of potassium. Secondly, control of intermediary protein and carbohydrate metabolism. In the first, which alone seems to concern us here, the desoxycorticosterones, synthetic compounds which only occur in the cortex of the adrenal gland in minute amounts, are chiefly concerned. It is well known that in adrenalectomized animals and in Addison's disease there is excessive loss of sodium in the urine and retention of potassium. This can be corrected by administration of desoxycorticosterone and a diet high in sodium content and low in potassium. A close structural relation exists between the compounds with cortin-like activity and the sex hormones, especially oestrin and progesterone, and it is found that pregnancy and pseudo-pregnancy prolong life in adrenalectomized animals.

The results of research on the adrenal have been reviewed by Swingle and Remington[20] but little has been done on any possible relation between adrenal disorder and the toxaemias of pregnancy. In a search for the causes of oedema and hypertension in eclampsia however this gland deserves attention, for we shall see later that there is yet no adequate explanation of either. Harrop and Thorn[155] showed that injection of suprarenal cortical extract into normal dogs caused sodium retention. Taylor, Warner and Welsh,[22] in their work on the effect of the sex hormone on the excretion of sodium in pregnancy and after delivery, found that in 2 cases there was after delivery "a pronounced divergence of the sodium and potassium lines which might indicate a return to normal from a previous condition of relatively low potassium and high sodium storage." "This could on theoretical grounds have been produced by hyperactivity of the adrenal cortex."

Ferebee[23] *et al* reported results of treatment of 13 patients with Addison's disease by desoxycorticosterone acetate or propionate. It caused a striking retention of salt and water and decrease in urinary excretion of sodium, chloride and water, the urine falling, in one case receiving a daily dose of 15 mg., to 410 c.c. in 24 hours. There was, as a result, a marked increase of extracellular and interstitial fluid. The blood-pressure rose to normal levels in 2 to

4 weeks and in 3 it rose gradually to 160/92, 160/110 and 146/108. An effect was not found from the use of progesterone in doses of 30 mg. daily for 7 or 8 days. Ten of the 13 patients treated by desoxycorticosterone developed clinical oedema varying from mild and transient puffiness of the face and ankles to massive anasarca. Altschule and Zamchek[24] report the case of a 43-year-old man who had had asthma for many years but no evidence of adrenal cortical insufficiency. On account of eczema, from which he had suffered for years, 5 grm. of sodium chloride by mouth daily and 1 c.c. cortin daily intramuscularly had been prescribed. At that time his blood-pressure was 120/80, and serum protein 5.94 grm. per cent. He received altogether 7 c.c. cortin in the daily doses. Marked oedema of his legs developed, which soon involved his whole body, and he was admitted to hospital in consequence. He then had rapid respiration, dyspnoea, orthopnoea, oedema of face, arms, legs and trunk, and effusion into his body cavities. In the urine there were large amounts of albumin, casts and small numbers of red blood cells. Blood-pressure was 200/100, serum protein 4.42 per cent. There was no evidence of congestive failure. The authors consider that the hypertension cannot be considered a consequence of increased blood volume. "The syndrome closely resembles that produced by a diffusely active vascular toxin." Swingle[20] also considers the rise in blood-pressure to be due to increased tone of the arterioles. Rodbard and Freed[25] showed that daily injections of 20 mg. of desoxycorticosterone acetate into (*a*) normal, (*b*) spontaneously hypertensive dogs, and (*c*) Goldblatt hypertensive dogs led to a rise of blood-pressure in 9 out of 12. The blood-pressure changes after cessation of the injections led a variable course; in some the hypertension remained for a considerable period, in others it fell rapidly or slowly to normal. Selye and Hall[26] found that following the administration of sodium chloride to rats treated beforehand by administration of desoxycorticosterone there is a more significant rise in the concentration of chlorides in the brain and blood than in animals not thus pre-treated. "It appears, therefore, from the experiment that desoxycorticosterone inhibits elimination of excess sodium chloride and that at least part of this salt is retained in the brain." Whether this leads to motor disturbances is a matter for further investigation. Swingle[20] points out that it is necessary to be cautious in the application of physiological *data* obtained from use of the synthetic desoxycorticosterone which is not elaborated in significant amounts by the cortex. Such striking results cannot yet be obtained by the use of natural extracts.

The Anterior Pituitary-like Hormone. Smith and Smith[27, 168, 169, 170, 171, 35] reported the presence of abnormally high levels of the anterior pituitary-like hormone in the serum and urine of patients with late pregnancy toxaemia and eclampsia, and that this increase can be demonstrated 5 or 6 weeks before other signs of toxaemia appear. They further state that the blood oestrin is diminished as well as the urine pregnandiol and that this "imbalance" between prolan, oestrin and pregnandiol may be an important factor in determining the onset of toxaemia. They found, however, normal values for serum prolan in 12 per cent of their pre-eclamptic and eclamptic patients. This finding has since been confirmed (Heim,[28] Tenney and Parker,[29] Rakoff[30]). Taylor and Scadron,[31] however, reported that the serum prolan in eclampsia was within normal limits. The general average and range, they say, for the prolan concentration of the serum and the 24 hours' excretion were not significantly

different from those of the normal controls. Selection of the severe cases with all the manifestations of pre-eclamptic toxaemia resulted, however, in the isolation of a group in which the prolan of the urine was a little high. As regards oestrin they found "probably significantly lower oestrogen values than in normal cases though there was nothing in the values obtained to distinguish the mild from the severe cases." As to pregnandiol (the excretion product of progestin in the urine) they confirmed the findings of Smith and Smith that it is diminished in toxaemia of pregnancy. Again, however, there were exceptions and it was found that a few toxaemic patients excreted more pregnandiol than normal.

Cope[32] failed to find any diminution of pregnandiol in toxaemic cases, including one of eclampsia. Taylor[33] treated 9 cases of pregnancy toxaemia with large doses of progesterone—up to 450 mg. and oestradiol benzoate 180,000 R.U. or a combination of these and failed to find any specific effect on the clinical course as indicated by blood-pressure, weight changes, output of urine and albuminuria. There was also little evidence of an increased rate of hormone excretion. Browne, Henry and Venning,[34] examining the excretion of prolan, oestrin and pregnandiol in the urine in 8 normal pregnant women, 4 cases of pernicious vomiting and 21 of late pregnancy toxaemia, reported that most of the late pregnancy toxaemias showed values for prolan which were within the normal range, tending to be low rather than high. Definite correlation of the level of excretion of either prolan, oestrin, or pregnandiol with the degree of toxaemia was not possible. These contradictory results are exceedingly confusing but it is interesting to note that Taylor[33] in 1942, and seeing that the Smiths' results have been so widely confirmed by other workers, seems to accept their position, for he writes: "There is then in toxaemia a tendency to low oestrogen and pregnandiol excretion, *probably a high chorionic gonadotrophin content of serum and urine*" (italics mine). Fractionation of the oestrogens, he states, shows that in toxaemia there is an increased percentage of oestrogenic activity attributable to oestradiol, a decreased amount of oestriol, and a low or absent oestrone content.

Assuming that these quantitative changes in hormone content of the serum and urine are accepted, what is their significance? Smith and Smith[35] suppose that the anterior pituitary-like hormone, the presence of which distinguishes human pregnancy from that of practically all other animals, plays an important part in the placenta's elaboration of progestin and oestrin just as prolan does in the case of the ovary. They consider the most plausible explanation of the high prolan levels in toxaemia to lie in a failing utilization of the hormone in the production of progestin and oestrogen so that it accumulates in the blood. Support for this view they find in the fact that in normal pregnancy a rapid fall in prolan occurs in the 3rd and 4th months coinciding with the rapidly increasing elaboration of oestrogen and progestin by the placenta. This accords with the idea that the anterior pituitary-like hormone is utilized normally for the secretion of oestrogen and progestin by the placenta, and that in being so utilized its level in the circulation is kept low. "On this basis one would place the primary aetiology of pre-eclampsia in whatever causes the placenta to be deficient in the utilization of anterior pituitary-like hormone for production of oestrogen and progestin." Taylor suggests that the low oestrin levels may be due to its greater utilization or to its rapid destruction with the possible formation of some toxic product. Browne, Henry and Venning[34] advance the hypothesis that the low

values for urinary oestrin and pregnandiol do not necessarily result from decreased production but may equally well be due to retention in the body from failure of their conjugation with glycuronic acid which presumably occurs in the liver, and of their excretion by the kidney. The reader will probably agree with all these authors that none of the explanations so far given is entirely satisfactory. It is pertinent, however, to recall the demonstration by Byrom[18] referred to on page 440 that gonadotrophic hormone as well as oestrogen is able to sensitize rats to vasopressin.

Dietetic Factors.

General Considerations.

Theobald[36] showed that it was possible, by feeding dogs on a lean meat and water diet, to cause a severe and even fatal degeneration of the liver and of the convoluted tubules of the kidney. These changes occurred whether the bitch was pregnant or not but more readily in association with pregnancy. In 1935, in a personal communication to the writer, he formulated his views as follows: "All the major and minor toxaemias of pregnancy are expressions of dietetic deficiencies and may be regarded as relative deficiency diseases. A diet apparently adequate for the mother is no longer adequate for the mother and foetus. While deficiency of the different vitamins and minerals all play a part, disturbance of the calcium metabolism is the most important single factor involved. This hypothesis relates morning sickness, hyperemesis gravidarum and excessive salivation to eclampsia, accidental haemorrhage and acute yellow atrophy of the liver."

McIlroy[37] writes: "From clinical experience I am firmly convinced that the way of research and progress lies not so much in a more or less lengthy search for illusive toxins as in the investigation of toxaemia as a deficiency disease."

One difficulty in accepting the view that dietary deficiency is an important cause of toxaemia lies in the fact that in Germany during the last 2 years of the 1914–18 war, when the civil population was grossly underfed, the incidence of eclampsia fell to 0.6 per 1,000 births as compared with 2.0 per 1,000 just before the war. Accurate figures regarding this fall can be obtained from Baden in Germany where eclampsia has been notifiable for many years. These have been analysed by Baader[38] who shows that during the war years the drop occurred steadily till 1918, after which there was a rapid rise. Baader shows, however, that the increase in 1919 and 1920 was due to the greater proportion of primiparae in the child-bearing population, and that when allowance was made for this by assuming that primiparae are 4 times more likely than multiparae to become eclamptic, the fall really continued till the end of 1920, during which period the effect of the blockade was still being felt. While this fall in the incidence of eclampsia has generally been attributed to the decreased consumption of flesh and fat other explanations have been put forward. It is noteworthy, for example, that during the war years there was no fall in the *mortality* from eclampsia, which continued as before to account for one death in every 4,000 births. This might possibly be due, as Baader suggests, to the milder cases of eclampsia having been overlooked on account of the scarcity of doctors, so that only the more severe and therefore the more obvious cases were reported by the midwives. Another factor may have been the more widespread employment of women in hard muscular work up till the time of delivery (Gessner[39]), and especially in the open air and sunshine, though this cannot explain the continued fall in the years 1919

and 1920, as according to Gessner most of the young women gave up their war work at the end of the war, in 1918. Bartholomew and Kracke[40] believe that the fall was due to the diet being deficient in fats and especially in cholestrin containing foods thus leading to a hypocholestrinaemia and consequently reducing the tendency to the formation of placental infarcts which they regard as the cause of eclampsia.

Calcium. Several studies have been reported on the value of calcium in reducing the incidence of toxaemia. Minot and Cutler[41] found that dogs were highly susceptible to carbon tetrachloride poisoning if kept on a diet low in calcium, i.e. lean meat without bones, but that they were immune to the poison if given a diet high in calcium and carbohydrate for 3 weeks before the poison was administered. If convulsions, which often follow carbon tetrachloride poisoning, had developed the injection of calcium salts brought about recovery. Theobald[184] has reported the results obtained in 100 women who at the beginning of the experiment were apparently healthy and not more than 24 weeks pregnant. They were divided into two groups of 50, to one of which calcium lactate gr. 20, together with 11,000 I.U. of vitamin D daily was given, the other group being kept as a control. Seven women in the treated group developed hypertension (blood-pressure 140 mm. Hg. or over, with or without albuminuria), and 17 in the control group. The difference is statistically significant. Mendenhall and Drake[43] found that only 2 out of 188 women (1 per cent) to whom calcium was administered in pregnancy developed toxaemia, whereas in a control series of 230 women 30 (13 per cent) became toxic.

Vitamin B. Observations on the geographical incidence of eclampsia have shown that eclampsia is common in countries like Japan, the Phillipine Islands and parts of China where the incidence of beri beri is high. Siddall[44] states that eclampsia is markedly more frequent in the south-eastern quadrant of the United States and that in this same quadrant occurs almost all the pellagra in the States. He found, however, that daily injections of 6.7 mg. of Vitamin B_1 (Thiamine chloride) for 10 days did not give any apparent benefit in patients with pre-eclampsia. Nixon, Wright and Fieller[45] found that in eclampsia the amount of vitamin B_1 excreted in the urine on admission to hospital is significantly lower than in normal pregnancy and that the concentration of vitamin B_1 in the placenta is also significantly below that of the placenta from normal cases. In the 1940 annual report of the Department of Obstetrics and Gynaecology of the University of Hong Kong, Gordon King[46] reports 155 cases of avitaminosis B_1 (beri beri) complicating pregnancy and labour, 135 (87 per cent) of which had a blood-pressure exceeding 130/70 including 16 cases of eclampsia. Assuming that the usual incidence of eclampsia is 1 in 500 pregnancies it is apparent that the incidence in beri beri is increased 50 times. Browne[47] however, was unable to find any diminution of the incidence of toxaemia from giving 960 I.U. of vitamin B_1 daily to 100 pregnant women as compared with a similar number of controls.

Protein. Tweedy[48] first promulgated the view that protein derivatives from the intestine are the cause of eclampsia. Normally, he said, they are neutralized by antibodies but in pregnancy these have also to neutralize products of foetal and maternal metabolism and may be insufficient for both purposes, so that protein poisoning results. On this view the treatment of toxaemia by a "low protein diet" is largely based. Dieckman[49] produced lesions in the liver resembling those in eclampsia —portal thrombosis, necroses and haemor-

rhages—by feeding raw meat to dogs and injecting tissue fibrinogen into the portal and peripheral circulations at the same time. He thought that in pregnancy there might be increased permeability of the intestinal wall so that larger protein molecules than amino acids could be absorbed, and that this fits in with the clinically observed reduction in the incidence of eclampsia by a low protein diet.

Recent tendencies have been rather in the other direction—to regard a *high* protein diet, especially one containing certain kinds of protein, as protective against toxaemia. Harding and Van Wyck[50] doubt if there is one controlled observation showing that inclusion of protein or fat in the diet in pregnancy leads to pre-eclamptic toxaemia or eclampsia. They did not find any ill effect following diets high in these constituents given to normal pregnant women or to patients with toxaemia. Strauss[51, 172, 173] believes that an inadequate protein intake, especially in view of the increased demand of the pregnant woman for protein of good biological value, leads to hypoproteinaemia and hence to oedema and pre-eclampsia. He treated toxaemia patients with a high protein diet and found that they improved—oedema diminished, weight decreased and headache and visual disturbances abated. Bibb[52] found a relation between hypoproteinaemia and the incidence of toxaemia, and that not many women had toxaemia without some previous hypoproteinaemia. Davis and Whipple[53] found that starved animals are very susceptible to liver injury from chloroform anaesthesia, and that the protection afforded dogs by a diet rich in casein was very complete. Goldschmidt, Vars and Ravdin,[54] in experiments on rats, found that a high protein diet prior to chloroform anaesthesia markedly reduces the incidence of hepatic cellular necrosis. Himsworth and Glynn[55] produced fatal necrosis of the liver in rats by a diet deficient in protein. The condition closely resembled acute yellow atrophy in man. The deficiency was due to a lack of casein in the diet, and giving methionine, an amino acid in which protein is moderately rich, was completely protective.

Clinical Experiments.

Such observations as those above mentioned were sufficient to suggest that the incidence of toxaemia might be significantly reduced by the administration of extra foodstuffs to pregnant women, and a number of such clinical trials have now been completed.

One of the first of these was carried out by Ross and his co-workers[56] on 54 primiparae in a charitable institute "under the supervision of a competent matron." The institution was run on a very limited budget and the diet contained an abundance of the cheaper items such as bread and cereals, while the supply of the more expensive foods, such as fresh fruits, milk, butter, eggs, meat and fish was greatly restricted. The estimated daily intake of proteins was 35 to 79 grm., only about 30 per cent of which came from meat, milk and eggs; 46 to 106 grm. fat; 102 to 266 grm. carbohydrate, and 964 to 2080 calories. To the diet of every other patient was added the following: 150 grm. skimmed milk powder, 20 yeast tablets, 15 drops of percomorphum oil, 2 grm. of bone meal, and 4 grm. ferrous sulphate. These supplied additional protein 60 grm., carbohydrate 75 grm., fat 2.5 grm., a total of 580 extra calories and also adequate amounts of vitamin A, B, D and E, as well as minerals, especially calcium, phosphorus and iron. The results were as follows:

Group I, control diet, normal delivery, 15 cases.

Group II, control diet, toxic delivery

(signs of pre-eclamptic toxaemia present at time of delivery), 11 cases.

Group III, enhanced diet, normal delivery, 18 cases.

Group IV, enhanced diet, toxic delivery, 9 cases.

Incidence of toxaemia in controls, 11 out of 26, or 42.3 per cent.

Incidence of toxaemia, enhanced diet, 9 out of 27, or 33.3 per cent.

They conclude that there was "no appreciable effect on the incidence of toxaemia." The most likely explanation of this, they consider, lies in the probability that the basic diet upon which the additional dietary factors were superimposed was not in the true sense of the term a deficient one.

The Toronto Experiment. This experiment, completed in 1941, was carried out in the Toronto General Hospital by Ebbs, Tisdall and Scott,[57] and involved 380 women. Only women who had not reached the end of the 6th month of pregnancy, and who had no major disease, were included. An analysis of the patients' food record was made at the beginning of the observation, and 2 months later. Patients were divided into 3 groups:

(*a*) Those receiving a poor diet throughout.

(*b*) Those having a poor diet, but supplemented for the purpose of the experiment.

(*c*) Those receiving a good diet and advice to ensure their making the best use of it.

If the diet was poor and income low, each alternate patient was selected for help from a special fund and supplied daily with 30 ounces of milk, one egg, one orange, one viosterol capsule containing 2,000 I.U. of Vitamin D and, once a week, with 16 ounces of factory-canned tomatoes and ½ pound of cheese. In addition, dried wheat germ, containing malt and added iron, were given. The extra food supplied to the patients in this group gave the following values: protein 45 grm., fat 46 grm., carbohydrate 60 grm., calories 840, calcium 1.45 gr., iron 15 mg., vitamin C 50 to 80 mg., vitamin B_1 350 to 400 I.U., and vitamin D 2,000 I.U. In the poor diet group there were 120 patients, in the supplemented group 90, and in the good diet group 170. The average duration of observation in the prenatal clinic was 4.4 months in the poor diet group, 4.7 months in the supplemented group, and 4.4 months in the good diet group. The past obstetrical histories of the multiparous patients were as follows (percentage of cases):

TABLE I.

	Poor diet group	Supplemented diet group	Good diet group
Abortions ...	13.1	4.7	9.0
Miscarriages ...	38.1	39.0	24.4
Prematures ...	10.7	20.3	13.3
Stillbirths ...	9.5	4.7	2.2

The incidence of complications in the 3 experimental groups were as follows (percentage of cases):

TABLE II.

	Poor diet group	Supplemented diet group	Good diet group
Anaemia	28.6	16.1	21.6
Pre-eclampsia	5.0	5.7	4.8
Toxaemia	7.6	3.4	3.0
Haemorrhage (prenatal)	5.9	5.7	2.4
Threatened miscarriage	8.4	1.1	2.4
Miscarriage	6.0	0	1.2
Premature birth ...	8.0	2.2	3.0
Stillbirth	3.4	0	0.6
Haemorrhage (during labour)	11.2	10.3	7.7
Endometritis	9.0	3.4	6.1
Mastitis	4.5	2.3	4.8
Breast abscess	3.0	1.1	3.0

The only items in Table II that concern us here are the second and third, i.e., Pre-

eclampsia and Toxaemia. Pre-eclampsia has not been reduced by the good or supplemented diets but "toxaemia" is considerably reduced. Indication is not given, however, as to what "toxaemia" includes, or as to how it differs from "pre-eclampsia," and one suspects that it includes cases of morning sickness or hyperemesis gravidarum. In any case a reference to Table I, in which the past obstetric histories are given, reveals that the incidence of abortion in column 2 is only one-third that in column 1, though both were on the same—an unsupplemented poor diet. The same criticism applies to the incidence of prematurity and stillbirths in the same table. These differences can only be due to chance, yet they are at least as striking as the differences in the incidence of "toxaemia" in the "poor" and "supplemented" groups.

People's League of Health Experiment. This experiment was organized by the People's League of Health[58] and carried out in 10 hospitals in London during 1938–39. In each hospital the women enrolled at the antenatal clinic were divided into 2 main groups. The women in one group received certain dietary supplements, while those in the other (alternate patients) were kept as controls. Within each of these groups the women were divided into primigravidae and multiparae, and these again into age groups—under 25, 25 to 30, and over 30. All women who were not in good health, or who were more than 24 weeks pregnant, were excluded from the experiment. The daily supplements given to the "treated groups" were as follows:—

Saccharated iron carbonate, gr. 18 (1.2 grm.), equivalent to 0.26 grm. ferrous iron; calcium lactate, gr. 30 (2 grm.), equivalent to 0.26 grm. calcium; minute quantities of iodine, manganese and copper; adsorbate of vitamin B_1, containing all factors of the B complex (B_1 content standardized at 200 I.U. per gram), gr. 15 (1 grm.); vitamin C (ascorbic acid), 100 mg.); halibut liver oil (vitamin A, 52,000 I.U. per gram, and vitamin D, 2,500 I.U. per gram), minims 6 (0.36 grm.).

At the conclusion of the experiment the records of the 5,021 women (2,510 treated and 2,511 controls) were examined and statistically analysed. The results in so far as toxaemia is concerned varied according to the standard of toxaemia adopted. At the beginning of the research it was decided to regard as toxaemic (*a*) women with blood-pressure of 140/90 or over, with or without albuminuria, oedema, etc., and (*b*) women who had no hypertension, but in whom the diagnosis was based on albuminuria. In the 1,530 treated primigravidae the incidence of toxaemia on this standard was 27.1 per cent, while in the control primigravidae it was 31.7 per cent, the difference being 4.6 ± 1.7 per cent, and statistically significant. This result was due to the dominating influence of the women aged 25 to 30 in whom the difference was 7.7 ± 2.6 per cent. At the younger and older ages the differences, though still favouring the treated groups, were statistically unimportant. In multiparae there was no difference between the treated and controls, the incidence of toxaemia being 21.8 per cent in both.

As these results were so indeterminate it was decided to adopt another standard of toxaemia, viz., not to regard as toxaemic any woman in whom the diagnosis rested on hypertension alone. The standard then became "albuminuria, oedema, etc., with or without, but generally with, hypertension." On this basis the incidence of toxaemia in the treated primigravidae was 5.4 per cent, and in the controls 7.4 per cent. The difference and its standard error was 2.0 ± 0.9, the odds therefore being nearly 40 to 1 against the

result being due to mere chance. In the parous women the incidence was 3.6 in the treated group, and 5.2 in the controls, the difference being 1.6± 0.9, and not statistically significant. (Table III.)

After studying the results outlined above the reader will doubtless conclude that while much careful work has been done, many more large-scale, carefully planned and statistically controlled experiments are necessary before final decisions regarding the importance of diet in prevention of toxaemias can be reached.

eclampsia and the "albuminuria of pregnancy" are due to liberation of the products of early autolysis of the placenta, and are especially associated with recent placental infarction. The infarction is due to interference with the maternal blood supply, the cause of which was obscure but was due to a toxin. The placenta is so constructed that if a part of it die the products liberated can pass directly into the blood stream. It thus arises that for the occurrence of toxaemia a circulation of blood round the poison generating foci is necessary and this

TABLE III.

People's League of Health Experiment Incidence of Toxaemia in Treated Women and Controls.

	No. of women	Hypertension only		Albuminuria with or without hypertension		Hypertension with Albuminuria ("pre-eclampsia")	
		No. of cases	Percentage	No. of cases	Percentage	No. of cases	Percentage
Primiparae:							
Treated	1530	332	21.7	83	5.4	69	4.51
Controls	1512	368	24.3	112	7.4	97	6.42
Diff. (C-T), and SE.	—	—	2.6±1.5	—	2.0±0.9	—	1.91±0.82
Multiparae:							
Treated	980	179	18.3	35	3.6	31	3.16
Controls	999	166	16.6	52	5.2	46	4.60
Diff. (C-T), and SE.	—	—	1.7±1.7	—	1.6±0.9	—	1.44±0.87
Total ...	5021	1045	—	282	—	243	—

SE. = standard error.

PLACENTAL TOXIN THEORIES.

There is much to be said for the assumption that if a toxin of some kind is the cause of eclampsia its source is primarily in the placenta. That it is not in the foetus is shown by the fact that eclampsia sometimes occurs in hydatidiform mole when there is no foetus (3 cases reported in the last 20 years). Again the placenta is suggested by the rapid subsidence of symptoms after foetal death.

Placental Infarction. Young,[59] as a result of anatomical and experimental investigations, claimed to have established that explains the absence of toxaemia in cases of accidental haemorrhage in which the placenta is completely detached by the blood clot or by other means.

Conversely the cases of accidental haemorrhage associated with a toxaemia are those in which part of the placenta remains attached for some time after the separation of the adjacent part by retroplacental bleeding. The necrosis of this part liberates the toxin. The experimental part of the investigation consisted in the injection into guinea pigs of dried sterile powder made from human placenta or saline solution of placenta that had been autolysed for a short

period. Convulsions were produced and also degenerative changes in the liver (thrombi in vessels, haemorrhages, fatty changes and focal necroses), and in the kidneys degeneration of the epithelium of the convoluted tubules. Not any untoward symptoms or pathological changes were caused in 20 control guinea pigs by injecting extracts of ovary or corpus luteum. In support of Young's theory, Miller,[60] examining the urine of 49 patients with placenta praevia for albuminuria and found it present in a catheter specimen in 25.5 per cent, and 3 of the patients developed eclampsia. Young has more recently (1927,[61] 1937,[62] 1942[63]), in a search for the factor that might lead to the placental damage, studied the reproductive history of patients with pregnancy toxaemia, and concluded that women with an eclamptic history commonly have resident in their body some morbid influence which is not inconsistent with good health between their pregnancies but which *is* inconsistent with the normal continuance of pregnancy to term. Many such damaged pregnancies end in abortion. Some end in premature birth or stillbirth but only in comparatively few does "this constant and imminent" X factor or "abortion factor" end in a toxaemic attack. The factor is not, he believes, a low reserve kidney or chronic nephritis. Evidence is adduced for the view that it is an endocrine disturbance, possibly a vitamin E deficiency which causes an upset in the prolan progesterone mechanism, and that it acts by interfering with the maternal circulation in the placenta leading either to placental infarction or to retroplacental haemorrhage or to both combined. It should be noted that toxaemia does not occur in threatened abortion and that Theobald[36] failed to produce any evidence of toxaemia by causing partial separation of the placenta in pregnant bitches.

Bartholomew and his colleagues (1932,[64] 1934[65] 1936[40]) claim that hypercholestrinaemia of pregnancy due to hypopituitary or hypothyroid activity and enhanced by a diet rich in cholesterol containing foods is the cause of toxaemia. Excessive storage of cholesterol in the arteries of the villi with resulting endarteritis is the predisposing cause of placental infarction, the exciting cause being the trauma of foetal movements causing thrombosis or rupture of a foetal artery. In the acute or subacute infarction thus caused autolysis takes place with liberation of peptone, guanidine and histamine as toxic split products of placental protein. They stress the importance in prophylaxis of restricting the use of fats and cholesterol containing foods and of giving thyroid extract. Young[59] has, however, shown conclusively that the epithelium covering the villi is nourished by the maternal, not the foetal blood. Infarction, therefore, cannot occur as a result of endarteritis in the vessels of the villi. We shall deal later with the evidence that guanidine and histamine play a part in the genesis of eclampsia.

Crush Syndrome. The view that placental infarction plays a part in the genesis of eclampsia has recently been considered by some to have gained support from the "crush syndrome" in which renal failure with oliguria or anuria follows a crushing injury of the limb. The main lesion in the kidney is a marked catarrh of the convoluted tubules sometimes amounting to actual necrosis. It affects their entire length but is most marked in the wide ascending limb of the loop of Henle and the second convoluted tubule. Myohaemoglobin pigmented casts are found in the second convoluted and collecting tubules (Bywaters and Dible[66, 68]). The cause of the tubular damage is not finally determined but it is suggested that it is due to acid metabolites

absorbed from the damaged tissues and excreted and concentrated in the urine. The tubular damage by allowing excessive and unselective absorption of the glomerular filtrate would account for the oliguria and the low concentration of such urine as is passed. Blockage of the tubules increasing the intra tubular pressure, regarded as all important by Morrison,[67] does not seem enough to account for the anuria as (a) only relatively few tubules are blocked in many cases (b) if blockage were the cause such urine as is passed should be clear (Bywaters and Dible[66]). Yet Bywaters[68] found that in rabbits muscle necrosis gives rise to all the signs and symptoms of crush syndrome except renal failure. Rabbit muscle does not contain any myohaemoglobin but fatal renal failure can be produced by injecting myohaemoglobin into rabbits acidified by ammonium chloride which aids its precipitation in the tubules. Until the cause of the renal failure is more clearly elucidated there would be little profit in speculating regarding its relation to eclampsia. It is, however, relevant to note that its clinical features are in many respects unlike those of eclampsia, e.g., there are no convulsions.

Before leaving the subject of placental infarction in relation to toxaemia it is well to note that not all observers agree that infarction is more frequent in toxaemia. Haffner[69] examined 400 placentas cut in sections 4 or 5 mm. thick, 73 of them being from toxaemic patients. In only about half the cases of toxaemia were there infarcts large enough to be visible to the naked eye, and in a large number of these the infarcts were few and small. On the other hand infarcts were found in 77 per cent of placentas from patients without toxaemia, and of these 30 per cent had fresh "haemorrhagic foci." Von Ravenstein[70] reported the results of his examination of 260 placentas cut also into slices $\frac{1}{2}$ cm. thick, noting the smallest infarct visible to the naked eye. Infarcts were found in 80 per cent of the 38 albuminuric placentas of the series, while of the non-albuminuric placentas infarcts were present in 66 per cent. Finally Clements[71] correlated the clinical and pathological changes in the placenta in 500 cases and concluded that there was no apparent increased tendency to necrosis (infarct formation) in the toxaemias of pregnancy. Markedly toxic patients and pre-eclamptics were observed without apparent placental change, while there were many placentas with advanced necrotic changes and a completely negative history.

Placental Ischemia. Arguing that the placenta is the excretory organ or kidney of the foetus, and that therefore it might be expected to behave as the kidney does when it is rendered ischaemic, as in the Goldblatt experiment, E. W. Page[72] conceives that any condition in which the uteroplacental circulation is unequal to the demand might lead to the production or over-production of a pressor substance by the placenta to keep up its blood supply. This would explain the increased incidence of toxaemia in hydatidiform mole, as the rapid growth of the mole needs a greater blood supply than the normal placenta of the same age. The primiparous uterus, too, is less able to develop a high degree of vascularity than one that has been pregnant before. In hydramnios with over-distension there is likely to be ischaemia, while multiple pregnancy would presumably also make greater demands on the circulation. Page has prepared an extract of fresh placenta which has marked pressor activity and can injure the capillaries. But Kellar and Sutherland[73] did not find any renin in the normal human placenta, and we shall see later that the renin hypertension mechanism cannot be the cause of the hypertension of pre-eclamptic toxaemia.

The Pressure Theory.

Paramore (1929,[74] 1932,[75]) believes that bio-physical forces occasion eclampsia and its preceding toxaemia. The more frequent occurrence of the disease in cases of twins, hydramnios, concealed accidental haemorrhage, and hydatidiform mole, in all of which the abdomen is over- and rapidly distended, indicates that the pressure caused by the stretched abdominal wall is a determining factor. This is confirmed by the prevalence of the disease in primigravidae; and particularly in active, muscular and well-developed primigravidae. He adds to this the increased volume, the greater mass of the blood in pregnancy, whereby congestion of compressed excretory viscera, induced by activity, can more readily occur—a condition which, he argues, is not present in women with large ovarian cysts. Postpartum eclampsia is explained by the effect of the biophysical forces operating during pregnancy and especially during labour on the viscera, particularly when the mass of circulating blood has not been sufficiently reduced by the parturient act.

Theobald[76] found that the intra-abdominal pressure in dogs and cats is not increased by more than 2 mm. Hg. during pregnancy. He concludes that it is probably not raised to any greater amount in man during pregnancy, except in the case of multiple pregnancy, especially if associated with hydramnios in a primigravida. It has been suggested that direct pressure by the pregnant uterus itself, especially when the woman lies on her back, may be a cause of eclampsia. It has been shown by Goldblatt and others that constriction of the renal artery, or of the aorta above the origin of the renal arteries, can cause ischaemia of the kidney and hypertension through the output of a pressor substance, renin, from the ischaemic renal tissue. Goldblatt[77] suggests that this has a possible application to the aetiology of eclampsia. "Since eclampsia occurs only in pregnancy when the uterus is greatly enlarged it is at least possible that the mass may press on the aorta or both renal arteries sufficiently to cause renal ischaemia. The suddenness with which the uraemic convulsive phase of eclampsia develops is in keeping with this idea." It is, however, often observed that the signs of pre-eclamptic toxaemia abate immediately after intrauterine death of the foetus, and before the uterus has become appreciably smaller. This fact alone seems to make any pressure theory untenable.

Pyelitis and Toxaemia.

Peters (1936,[78] 1938[79]) has in recent years claimed that pyelitis and pyelonephritis are important factors in the causation of pre-eclamptic toxaemia and eclampsia. Of 93 patients with pyelitis complicating pregnancy 25 developed hypertension or oedema or both, and of 320 patients with toxaemia 41 (13 per cent) had pyelitis. Further, of 25 autopsied patients with vascular or renal disease that first manifested itself during pregnancy 11 were found to have pyelitis and hydronephrosis. It is supposed that pyelitis may cause eclampsia either by causing infection and infarction of the placenta or because, being accompanied by dilated ureters and hydronephrosis, it might lead to ischaemia of the kidneys and the emission of renin as in the Goldblatt experiment. Blalock[80] states that hypertension can be caused in dogs by obstructing the outflow of urine sufficiently to cause hydronephrosis and that the hypertension is not abolished by denervation of the kidney. Hayes[81] states that he finds the back pressure phenomena, hydronephrosis and dilatation of the ureters much more marked in pre-eclamptic and eclamptic patients and in those with hyperemesis gravidarum. He catheterized the

ureters and cured all these cases, including 19 cases of hyperemesis gravidarum. In 6 patients with eclampsia the fits ceased a few hours after the ureters were drained.

Prather and Sewell[82] conclude from a study of their *data* that pyelitis is not a cause of toxaemia of pregnancy. Baird[83] found that patients with marked ureteral stasis with or without urinary infection have a normal or low blood-pressure and are not subject to albuminuria of pregnancy. He notes too that pyelitis seldom developed in women in whom albuminuria and a rise in blood-pressure arise during pregnancy and that in the few cases in which urinary infection did develop during pregnancy it had been transitory. Mussey and Loveday,[84] among 92 patients with pyelitis in pregnancy, had only 3 in whom the pyelitis was accompanied or followed by acute toxaemia; 30 women who had pyelitis of pregnancy were under their care during one or more subsequent pregnancies without showing evidence of recurring pyelitis and only 2 of these developed toxaemia. They consider that these results indicate that "acute pyelitis of pregnancy, when treated promptly, is not prone to cause pre-eclamptic toxaemia or eclampsia, and that following one attack of acute pyelitis of pregnancy the majority of such women do not exhibit symptoms of residual renal disease." McLane[166] too (1939) failed to find any higher incidence of toxaemia among his cases of pyelitis. The incidence was 10 per cent among 98 cases of proved antepartum pyelitis, which was the same as in the whole clinic population.

Allergy.

Veit,[85] Weichardt[86] and others suggested that the entry of placental cells into the mother's circulation gave rise to the formation of antibodies and that this was the cause of eclampsia. Rosenau and Anderson,[87] to test their hypothesis that toxaemia of pregnancy might be a condition of hypersusceptibility, injected into guinea pigs extract of guinea pigs' placenta that had been autolysed one hour at room temperature. After 22 days the guinea pigs were inoculated with placental extract autolysed for 3 hours. The guinea pigs got marked anaphylaxis symptoms. Rosenau and Anderson[87] concluded that the mother might be sensitized by the autolytic products of the placenta. Leith Murray[88] repeated Rosenau's experiments but used fresh unautolysed liver; his results "seemed to prove that it was the autolysis rather than the pure placental element that caused the anaphylactic symptoms." Johnstone[89] produced symptoms of anaphylaxis (convulsions, blanching of the ears, dyspnoea, etc.) in rabbits by injecting filtered fresh juice of normal unautolysed human placenta 12 to 23 days after a sensitizing dose, but he got negative results from injecting homologous placental extract in rabbits and guinea pigs. His results seemed, he says, "to support the view that there is no evidence of anything in the nature of anaphylaxis, so far as we at present understand the subject, in the commoner manifestations of the toxaemias of pregnancy."

Knepper[90] claims to have produced the typical histological changes of eclampsia in dogs by injecting unsensitized horse serum followed by posterior pituitary extract. The lesions included peripheral hepatic necrosis and degeneration of the kidney tubules. Jegorow (1934,[91] 1935[92]) is also an enthusiastic advocate of the allergic theory He supports his views by ingenious arguments but not by any experimental work. "There is no toxin; the cause of eclampsia is allergy of the pregnant woman whose organism is gradually sensitized against the normal foetus and placenta." He attaches great importance to the allergic condition of the vegetative nervous system. "All

the symptoms of eclampsia, especially the raising of the intracranial pressure and the blood-pressure, the fits, oedema, nephropathia, acidosis and other biochemical changes in the organism of the pregnant woman, are fundamentally the consequence of this allergy." Seitz,[93] however, opposes Jegorow's views and points out that the characteristic peculiarity of the allergic reaction is that it always tends to recur if the same injury attacks the body as, for example, in hay fever. "Can one allege that of eclampsia, which is a disease chiefly of primiparae and recurs only in 2 or 3 per cent?" This would appear to be an unanswerable argument.

The Rôle of Infection.

Delore[94] first suggested that eclampsia might be of microbic origin. As evidence there was the high temperature of eclampsia, the fact that it sometimes seems to occur in epidemics, and that its high mortality resembled that of other infectious diseases. Talbot[95] found dental sepsis in all of 97 cases of toxaemia. He considers that it may cause placental infarcts. "Toxaemia is not usually the result of a single acute infection but of a long-standing infection with oft-repeated emboli of bacteria." He is "aware that many of the ideas advanced by him are unsupported by laboratory technique." Toombs[96] says that infective foci in gums, teeth and nasal accessory sinuses are prevalent. In pregnancy resistance is lowered and the placenta is an ideal site for development of secondary infection. The convulsions and other manifestations of the eclamptic state may be accounted for by the action of the circulating bacterial toxin on the sympathetic nervous system. There are abundant opportunities for testing the truth of this theory now that pre-eclampsia is so often treated by Caesarean section with its opportunities for obtaining sterile placentas. Yet no one has reported any positive cultures from these placentas.

Chemical Poisons.

A good case can theoretically be made for the view that eclampsia is due to the action of certain organic poisonous substances. Of these most attention has been paid to guanidine, histamine and tyramine.

Guanidine and methyl guanidine. Guanidine is a substance which normally occurs in traces in the blood but in much larger amounts in renal insufficiency. It appears to behave as the physiological antagonist of calcium which inhibits the action of guanidine on the neurological apparatus (Bodansky[97]). Noel Paton showed that guanidine may lead to hypoglycaemia probably by a toxic action on the liver, and synthalin (deca methylene diguanidine) was used in pre-insulin days to lower the blood-sugar in diabetes, but often produced toxic effects such as nausea, vomiting, diarrhoea, and jaundice. Major[98] found a striking pressor effect from injecting methyl guanidine sulphate in doses of 0.05 to 0.1 grm. per kilo of body weight. The blood-pressure rise so caused persisted 4 or 5 hours and was accompanied by tremors, slowing of respiration and other evidence of toxic effect. Major and Weber[99] reported that in normal blood the concentration of methyl guanidine was not over 0.2 mg. per cent, and that in most cases of hypertension they had found, making allowances for creatine in the colour reaction, an increase of methyl guanidine or some other guanidine compound, and that in dogs convulsions occurred when the concentration in the blood was 1 mg. per 100 c.c. or over. Andes and Myers,[100] in 8 normal women just before delivery, found the range of guanidine from 0.17 mg. to 0.22, average 0.20; 112 estimations done on 37 cases of toxaemia of pregnancy showed that if the toxaemia were

mild the concentration was about the same as in normal cases. In severe toxaemias it showed a rise, the high value remaining as long as the toxaemia persisted, and convulsions were usually associated with high values. A direct relation was not found between the level of blood-pressure and the degree of hyperguanidaemia, though in general the patients with higher blood-pressure showed higher guanidine values. The *increase in guanidine always followed the rise in blood-pressure* and so could not be its cause. Minot and Cutler[41] reported an increase of guanidine or guanidine-like substances in the blood of dogs during the intoxication caused by carbon tetrachloride. The increase was soon followed by a fall in blood-sugar going on to extreme hypoglycaemia, with nervous excitability, vomiting, diarrhoea and frequent haemorrhages. Calcium salts protected and cured them. In 8 cases of pre-eclamptic toxaemia and 4 of eclampsia they found hypoglycaemia, i.e., a fasting blood sugar of 60 to 75 mg. per cent in the pre-eclamptics, compared with 90 to 105 in normal controls. In eclampsia blood sugar was 37 to 52 mg. per cent. In both groups guanidine was high—0.50 to 0.85, compared with 0.25 to 0.40 mg. per cent in normal women. Ten c.c. of 10 per cent solution of calcium gluconate restored the blood sugar to normal in 24 hours and was also followed by general improvement and a fall in blood-pressure. The guanidine concentration, however, was not affected by this medication. Soon after delivery the guanidine returned to normal. In a case of eclampsia with fits the patient became blind and almost unconscious. The blood sugar was 52 mg. and blood guanidine 0.64. "We believe that the data show that in certain types of liver disease and in eclampsia the same abnormalities of blood chemistry were present as were seen in dogs during the intoxication caused by carbon tetrachloride." Pfiffner and Myers[101] introduced a colorimetric method of estimating guanidine which enabled them to exclude interference by creatine. They applied it to a few normal and hypertensive bloods and got a "slight but definite" increase in the colour reaction with hypertensive blood. They consider that their results confirm Major's original findings. Malméjac[102] also found hyperguanidaemia in eclampsia and considers that there is in eclampsia a "glandular dyssynergy" which shows itself by hypocalcaemia and the accumulation in the blood of toxic bodies like guanidine. He suggested that this was due to a parathyroid deficiency and advocates intensive calcium and parathyroid medication. De Wesselow and Griffiths,[103] making allowance for creatine in their determinations, concluded "it remains uncertain whether the so-called "guanidine" present in the blood is actually guanidine and whether it is present as guanidine or as a substituted methyl compound." In 3 cases of pre-eclampsia and one of eclampsia the guanidine content of the blood was low. In the eclamptic it was only 0.018 mg. per cent. "It does not seem possible to invoke the convulsive action of guanidine described by Major in explanation of the eclamptic convulsions." They also found that in individual hypertensives there were gross fluctuations in blood-guanidine without corresponding changes in blood-pressure.

Titus, Messer and McLellan[104] claimed to have demonstrated a suddenly occurring hypoglycaemia preceding eclamptic fits, and believed this to be correlated with high blood-guanidine. They injected guanidine and dimethyl guanidine into rats and guinea pigs and caused degenerative changes in the liver "suggestive of the early stages of hepatic degeneration, including interstitial haemorrhages, periportal thrombosis and focal necrosis, and in the kidneys cloudy

swelling of the convoluted tubules. Stander[105] examined the blood-guanidine in 12 eclamptics and 3 normal controls. In the normal women he found the average value to be 0.33 and the range from 0.22 to 0.40. In the 12 eclamptics the average was 0.39 and the range 0.26 to 0.40. He does not agree with Minot and Cutler and Titus that there is a tendency to hypoglycaemia and a definite elevation of blood-guanidine in eclampsia. "In our cases a normal blood sugar or an actual hyperglycaemia is seen far more often than hypoglycaemia." Neither, he thinks, does calcium therapy help. "It does not seem indicated on the basis of blood sugar or blood guanidine content as hypoglycaemia and increased guanidine are not the usual findings in eclampsia." Krieger[106] in 30 cases of eclampsia failed to find any appreciable rise in blood-guanidine. Finally Wodon[107] found that experimental intoxication with guanidine is accompanied by the same modification of acid base equilibrium of the blood as in eclampsia—a lowering of the alkali reserve and a deviation of the *p*H of the blood to the acid side.

The one point that is clear from this volume of contradictory evidence is that the *rôle*, if any, of guanidine in toxaemia will not be settled till a method is evolved of determining the concentration of guanidine in the blood by direct chemical means rather than by colorimetric methods in which other substances may interfere with the colour reaction.

Histamine. Histamine occurs in normal tissues but is loosely held by some mechanism that prevents it being liberated at a rate comparable with that resulting from its injection (Best and McHenry[108]). Kenneth Harris[109] found that samples of human skin contained 10 mg. per kilo. It can be formed by removal of the carboxyl group from the naturally occurring amino acid histidine by bacterial decomposition, and Mellanby and Twort[110] isolated from the faeces a micro-organism that can produce histamine in this way. Hofbauer and Geiling[111] studied the effects of injecting histamine intravenously or intracardiacally in pregnant guinea pigs and cats. The immediate effect was to cause tetanic contraction of the uterus with engorgement of the vessels. In guinea pigs, but not in cats, partial separation of the placenta took place. Hofbauer later[112] pointed out the similarity in the blood chemistry of human eclampsia and acute histamine poisoning. Notwithstanding, Best and McHenry[108] wrote "in the case of eclampsia, as in various other conditions we have considered there is as yet complete absence of satisfactory direct evidence that histamine plays any significent *rôle*," and again, "there is at present (1931) no conclusive evidence that histamine is the causative agent in any pathological condition."

Further "direct evidence" has been lately obtained by Kapeller-Adler[113, 183] who found that histidine, which is a constituent of the urine in normal human pregnancy, the excreted amounts varying from 15 to 50 mg. per cent, is considerably less in severe pre-eclampsia and may be only present in traces or completely absent. On the other hand histamine was found in large amounts in the urine in severe pre-eclamptic toxaemia, hyperemesis gravidarum, and premature separation of the placenta. She quotes Werle as finding in animal tissues, especially the kidneys, an enzyme, decarboxylase, which can form histamine from histidine in absence of oxygen. The amount of histamine present in the urine therefore depends on the balance between the action of decarboxylase and histaminase, an enzyme that can destroy histamine. Though there are certain resemblances between the pathological effects in the organs and tissues obtained from the experimental injection of hista-

mine and those of eclampsia, especially increased capillary permeability, one of its most outstanding effects is to lower the blood-pressure. Indeed, the most useful method for the qualitative and quantitative determination of histamine is that based on the lowering of the blood-pressure of an etherized and atropinized cat. It will also be noted that Kapeller-Adler does not claim any increase of histamine in the blood. Dorothy Potter[114] compared eclamptic serum with a standard solution of histamine phosphate and failed to find any action on the guinea pig's uterus—another standard test for histamine.

Tyramine. This is a toxic pressor substance derived from the amino acid tyrosine from which it can be formed by action of certain bacteria, especially those of the coliform group and haemolytic streptococci. Johnson[167] (1940) attributes to it a leading role in the causation of eclampsia. He believes that venous stasis, caused in the placenta by the upright posture and other disturbances of pressure (multiple pregnancy, hydramnios, etc.), leads if prolonged to death of some chorionic villi and the production in them of tyrosine. Circulating bacteria produce tyramine from the tyrosine in the dead tissue and the tyramine being absorbed causes hypertension and capillary spasm. In support of this theory Johnson has reported that injection of tyramine into the portal circulation of animals causes peripheral liver necrosis. As, however, tyramine causes spasm of the efferent glomerular arterioles (Goldring, Chassis, Ranges and Smith[115]), which is absent in pre-eclamptic toxaemia, it is unlikely to be the cause of this condition.

Constitutional Predisposition to Eclampsia.

It has long been thought by many observers that there is in certain women a constitutional predisposition that makes them more liable to develop hypertension and eclampsia. Ayman[116] from a study of the personality of 182 subjects, normal and hypertensive, found indications that hypertensive subjects tend to have a distinct type of personality, characterized by increased psychomotor activity with a large and steady output of energy. Vorzimer *et al*[117] conclude from a study of their records that in a large majority of instances toxaemia of pregnancy occurs in women with a constitutional habitus in itself a manifestation of endocrine disturbance. The body weight and the weight height ratio are higher, and the build tends to be short, thick and stocky. There are abnormalities of hair distribution, facial characteristics and other bodily changes suggestive of acromegaly, such as enlargement of the nose, hands and feet; the pelvis is often of android or anthropoid type and the basal metabolic rate tends to be low. "In 98 per cent of our patients with toxaemia of pregnancy there were one or more endocrine stigmas, and in a large majority there were two or more. Only 15 per cent of normal controls had any, and only 3 per cent had more than one." Maltby and Rosenbaum[118] investigated the electro-encephalographic findings and family histories of a group of 17 patients in whom a diagnosis of eclampsia had been made at periods varying from 1 week to 5 years previously, with the result that 77 per cent of the 17 eclamptic women had electro-encephalograms indicative of cerebral dysrhythmia." Fifty-eight per cent of this series gave a family history of "convulsive disorders."

Theobald[174] produced figures from the Registrar General's Decennial Report for England and Wales for the 10-year period 1911 to 1920 which, in his opinion, threw considerable doubt on the accuracy of the view that pregnancy toxaemia could cause chronic nephritis or even disease of the

circulatory system. The figures in the Report showed that during these years the mortality curves from Bright's disease, including hypertensive cardiovascular diseases, followed the same upward and downward trends as those for men, and that there was no significant difference between the mortality rates from these diseases for married and single women up to the age of 55. Theobald's contention has never been adequately answered and must be taken as correct. The only convincing explanation of his findings is that those women who develop hypertensive cardiovascular disease after toxaemia were originally predisposed to it, and would have developed it even though they had never become pregnant. Further evidence in support of this view is afforded by a recent study by Isenhour *et al*[119] of the blood-pressures of 1,800 women aged 20 and over, 900 of whom were parous and 900 nulliparous. They found that the incidence of hypertension, i.e., a blood-pressure of 140/90 or over, was slightly higher in the nulliparous than in the parous women at all ages. This shows that to all intents and purposes, the patients having hypertension following toxaemia of pregnancy are the same who would have developed hypertension if they never had been pregnant. It also seemed likely that pregnancy neither aggravates latent hypertension nor makes it obvious earlier, because they did not find any increase in the incidence of hypertension in the younger age groups of the parous as compared with the same groups of the nulliparous women. In their opinion too, the results show that toxaemia of pregnancy occurs for the most part, if not exclusively, in women whose vascular systems are endowed with a tendency towards hypertensive disease.

The Cold Test in Pregnancy. This was introduced by Hines and Brown in 1933[120] They hoped that by its use it would be possible to pick out those individuals who had a constitutional predisposition to hypertension. The test is carried out as follows: The person to be tested is kept lying down for 20 minutes or more, the blood-pressure being recorded every 5 minutes until it has reached a basal level. The opposite hand is then placed in a bath of ice water at 4° or 5°C. for 2 minutes, and the systolic pressure is recorded every 30 seconds during that time. The hand is then removed from the bath and dried and the pressure recorded every 2 minutes till it returns to the base level. Three measurements were regarded as important, viz., the peak or ceiling (the highest pressure observed while the hand is in the bath); the range (the difference between the peak and the basal pressure); and finally the time elapsing till the pressure returns to the base level. The highest normal peak is placed at 145 mm. Hg.; the highest normal range has been variously placed at 20, 22, or 30 mm.; while the time taken to return to normal should not be more than 2 minutes. As Hines and Brown carried out their tests on patients who were not pregnant it was impossible to say whether hyper-reactors would ultimately develop clinical hypertension without following them up for a long period of years, which has not been done. In pregnancy, however, onset of the hypertensive type of pre-eclamptic toxaemia only takes a few months and it has therefore been thought possible to pick out early in the pregnancy those women who, because of a constitutional predisposition, would later develop this disorder. Dieckmann[121] used the test in 152 normal pregnant women. Regarding a range of 30 mm. or more as abnormal, he found that 90 patients were hyper-reactors and of these 31.1 per cent developed toxaemia, while of the 62 patients who gave a normal reaction only 11.3 per cent did so. Browne[122] used the test in 52 normal primigravidae and

reached the following conclusions: a peak of 150 or over is a fairly good but not invariable indication that hypertensive toxaemia will develop later. Neither the range nor the time taken to return to the base level seemed to be of any value. A high basal pressure, however, did seem to be of value for the mean basal pressure among the patients who developed toxaemia was 116, while among those who did not develop toxaemia it was only 108, a difference that was statistically significant. Reid and Teel,[123] as a result of a study of 159 observations on 34 pregnant women, were unable to support the suggestion that the test might reveal impending toxaemia.

Rhesus Factor in Toxaemia.

As eclampsia occurs in hydatidiform mole (the writer has found 3 cases reported in the literature since 1924) in which a foetus is absent, and in which there is no foetal blood in the chorionic villi, and as the development of an antibody in the mother depends on the presence of an antigen in the foetal red-blood cells it would seem to be extremely unlikely that there would be any special association between the Rh factor and pre-eclamptic toxaemia. Might the hydatidiform mole, however, be regarded as an extreme degree of erythroblastosis—compare the dropsical chorionic villi with the oedematous placenta of erythroblastosis? We do not know at what period in the molar pregnancy the foetus disappears. It has probably been present at some time after embedding as a trophoblast has developed. May the foetus have been Rh positive and caused the development of antibodies in the mother before its death and disappearance? If this were so one would expect the mother who gives birth to a hydatidiform mole to give birth in other pregnancies to erythroblastotic infants, which she rarely does.

Javert,[163] however, states that toxaemia is present in 31 per cent of hydrops cases. Schwartz and Levine[164] investigated the blood of 2 eclamptic mothers. Both were Rh positive and of 5 cases of severe pre-eclamptic toxaemia, in 4 the maternal blood was Rh positive. On the other hand, of the 7 cases of definite foetal erythroblastosis in 5 the mother had "mild to moderate pre-eclampsia." Schwartz and Levine[164] "feel that the theory of iso-immunization as the important factor in the aetiology of eclampsia should not be discarded without further investigation. Further studies are indicated taking into account also the possibility of iso-immunization by blood factors other than Rh." The matter could be settled by examining the blood of eclamptic women for anti Rh, anti A and anti B agglutins.

The Kidney in Toxaemia.

Histological Changes. Owing to the researches of Lohlein,[124] Fahr (1920,[125] 1925,[126] 1928[127]), Bell[128] and Baird and Dunn[129] we now have a very complete picture of the renal changes in eclampsia. The following description is taken from Baird and Dunn's paper: "The glomeruli were slightly enlarged. They were denser and more solid than normally and notably bloodless. Many of the capillary loops in each tuft appeared swollen and solid without lumen. Sometimes this might be due to blockage by swollen endothelial cells which might also be increased in number. There was a practically universal but uneven thickening and reticulation of the capillary basement membrane and the glomeruli in all cases were notably bloodless. "Another notable feature of the lesion was its diffuseness in the sense that every tuft is involved." In the majority of cases the first convoluted tubules were fairly normal apart from varying degrees of early

autolytic change which could also possibly be interpreted as early cloudy swelling. Necrosis was not noted in any. "The conditions contrast, therefore, with those in septic infection or pneumonia where toxic agents are at work and cloudy swelling or fatty degeneration are well marked. So far as it goes this does not support the view that there is in eclampsia a protoplasmic poison circulating in the blood. Such alterations as do occur in the tubules may arise directly or indirectly as a result of the glomerular lesion." Opinions differ as to whether the glomerular lesion is degenerative or inflammatory. It is probably best regarded as a response to a stimulus of some kind. According to Bell the thickened basement membrane is not a homogeneous structure merely thickened by oedema or by a hyaline change but is composed of fibres laid down in parallel layers representing an actual increase in substance. The swelling of the endothelial cells is in Bell's view probably due to a toxic substance and this may also cause the thickening of the basement membrane. Similar changes have been described by McGregor[130] in essential hypertension. Experiments by Blount[131] suggest that the cause is increased intravascular tension. He transplanted pituitary anlages from one amphibian embryo into the side of the body of another at the same stage. The grafts developed and so caused pituitary hyperfunction. Two such grafts in each embryo produced the "triple pituitary host." Fifteen hosts were used and 15 controls. The "individual" develops hypertension accompanied by vasoconstriction. In each of the 15 hosts the basement membrane of the glomerular capillary tuft showed thickening and there was no change in the controls. It can, therefore, be definitely stated that in the amphibian the high blood-pressure appears first. This suggests that hypertension is the cause of the thickening of the capillary basement membrane in toxaemia. Bell,[132] however, found similar changes in 3 cases of lipoid nephrosis in which the blood-pressure was normal. "The basement membrane is uniformly thickened and multilayered and some of the capillaries are partially or completely obstructed by swollen endothelium or by thickened basement membrane." This would seem to show (1) that the glomerular changes are not due to rise of blood-pressure and (2) that the glomerular obstruction is not the cause of the hypertension of toxaemia.

It should be noted that Page and Cox[133] have recently cast doubt on the specificity of the glomerular lesion. In a control group of 11 women known to have no toxaemia they found in 5 appreciable degrees of thickening of the basement membrane. One of these had prolonged streptococcal sepsis, one acute pyelitis, one lobar pneumonia, one pancreatic necrosis and broncho pneumonia and one encephalitis and pneumonia. The possibility that one or two of them had had pre-eclamptic toxaemia in a previous pregnancy, passing unrecognized, had not been excluded.

Renal Function in Toxaemia. By the use of inulin,[186] a polysaccharide which is filtered only at the glomeruli and not reabsorbed from the tubules and the clearance of which is, therefore, a measure of glomerular filtration, and diodrast[186] an organic iodine compound which is excreted chiefly by the tubules and measures the tubular excretory function and effective renal blood flow several workers (Chesley *et al*,[187] Wellen, Welsh and Taylor,[135] Corcoran and Page[185]) have measured the rate of glomerular filtration and the effective renal blood flow in normal and toxaemic pregnancy. In normal pregnancy Wellen, Welsh and Taylor[137] found glomerular filtration and effective renal blood flow to be unaffected, but in 13 patients with true pre-eclamptic toxaemia, including 2 eclamptics,

they found [135, 137] that glomerular filtration is somewhat reduced as compared with postpartum values. This may, in their opinion, be due to spasm of the afferent glomerular arterioles or to the thickening of the basement membrane of the glomerular capillaries above described, with increased resistance to filtration. As a rise in filtration rate occurs soon after delivery, however, it is probably due to arteriolar spasm. The effective renal blood flow in toxaemia was found to be normal or even above normal. This shows that renal ischaemia is not an essential factor in causing the hypertension of pre-eclamptic toxaemia. There was no constriction of the efferent glomerular arterioles in pre-eclamptic toxaemia during the pregnancy but it appeared after delivery if the patient developed chronic hypertension.

Oedema.

General Considerations.

Oedema is a common but not invariable accompaniment of pre-eclamptic toxaemia. Many authors, in spite of the fact that some of the worst cases of eclampsia are unaccompanied by any oedema, ascribe to it an important *rôle* in causation of the convulsions. Arnold and Fay,[138] for example, as a result of naked eye and histological examination of the brain in eclampsia, stress the prevalence of widespread cerebral oedema. Rowntree[139] produced tonic and clonic convulsions in dogs and other animals by administering by stomach tube 50 c.c. of water per kilo of body weight every half hour. He found that the intracranial pressure was raised. The only postmortem change found was oedema of the connective tissue of liver, kidneys and brain. If hypertonic sodium chloride was given intravenously the symptoms were relieved and recovery took place, and if given at the same time as the water, intoxication could be prevented. The blood-pressure was not raised unless posterior pituitary extract was given at the same time (Weir, Larson and Rowntree[181]), but convulsions occurred though the blood-pressure was not raised. Kubie[140] found that if spinal drainage were done on the Rowntree dogs during water administration cerebral irritation and convulsions did not occur. Elsberg and Pike[175] (1926) showed that hydrated animals were more susceptible to convulsant drugs than normal and that dehydrated animals required twice the dose of absinthe to produce convulsions that normal animals did.

A latent oedema, shown only by abnormal increase of weight (Cummings,[141] Siddall and Mack,[142] Arwyn Evans[143]), or by measurement of extracellular water (Chesley and Chesley[144]), may be the earliest sign of pre-eclamptic toxaemia. The sign is, however, unreliable in that only about 50 per cent of those who show an abnormal increase of weight ever develop pre-eclamptic toxaemia, and on the other hand pre-eclamptic toxaemia may develop without any warning in the form of latent oedema. There is no evidence that oedema can, of itself, cause hypertension. In lipoid nephrosis and in nutritional oedema hypertension does not occur, and we have already seen that in Rowntree dogs water intoxication did not cause hypertension unless posterior pituitary extract was also given. On the other hand posterior pituitary extract did not give rise to convulsions unless water intoxication was caused at the same time. (Weir, Larson and Rowntree[181]).

Genesis of Oedema.

In attempts to explain the genesis of oedema the following possibilities must be considered in addition to the posterior pituitary antidiuretic factor which we have already rejected as insufficient to account

for it. The same applies to the decreased glomerular infiltration which we have seen is a feature of pre-eclamptic toxaemia.

(*a*) Lowered plasma osmotic pressure through hypoproteinaemia.

(*b*) Increased venous and capillary pressure.

(*c*) Increased capillary permeability.

(*d*) Sex hormones influencing electrolyte and fluid balance.

(*e*) Factors that are merely contributory in a minor degree, such as anaemia of pregnancy, increased plasma volume, etc.

(a) *Lowered Plasma Osmotic Pressure.* Starling[145] demonstrated the part played by the colloid osmotic pressure of the plasma proteins in counterbalancing the mechanical effect of the intracapillary pressure. A low level of the plasma or serum proteins is now a well-recognized cause of nutritional oedema, and in pregnancy the increased demands of the foetus and the maternal organism, the dilution of the plasma reaching as much as 25 per cent by the 36th week, and a suboptimal intake of first-class protein in the diet, might well lead to a lowering of the plasma proteins to the "critical level" (less than 5.2 per cent total proteins, or albumin fraction under 2.3 per cent) below which oedema is likely to occur. Studies of the plasma proteins show that in normal pregnancy they are lowered in the later months by about 9 per cent (Plass and Bogert,[146] Plass and Matthews[147]). As the albumin fraction of the total protein has about four times the osmotic pressure of the globulin fraction, its estimation is of importance in addition to that of the total proteins. Dieckmann and Kramer[188] give the following figures for serum proteins in normal and toxaemic patients, serum protein being usually estimated instead of plasma proteins as the latter includes fibrinogen which is about 0.43 per cent of the plasma proteins but has little or no osmotic value. In normal women not pregnant the total serum protein is 7.5 (range 6 to 8.3); in normal pregnancy 6.5 (range 5.75 to 7.9); albumin 3.72 and albumin globulin ratio 1.33. In pre-eclamptic toxaemia with oedema the total serum protein is 6.22, serum albumin 3.24 and the albumin globulin ratio 1.04. These figures are, therefore, well above the "critical levels." Strauss (1935,[51] 1937,[172] 1939[173]), however, the leading advocate of the *rôle* of hypoproteinaemia as the cause of oedema and hypertension in toxaemia, stresses the importance of even a moderate lowering of the colloid osmotic pressure if sodium salts, especially sodium chloride or bicarbonate, and water are taken in excess. Patients may have plasma protein below the "critical level" without oedema, because they did not ingest the necessary salt and water to allow the formation of oedema. On the other hand if there is a large salt and water intake they may get oedema with a plasma protein well above the so-called "critical level." He, as well as Harding and Van Wyck,[50] was able to cause serious aggravation of the symptoms of pre-eclamptic toxaemia by giving 18 grm. sodium chloride or 23 grm. sodium bicarbonate, the sodium causing parallel retention of water in the tissues. There were significant weight gains, increase of visible oedema, and rise in blood-pressure with increasing albuminuria, and in 3 patients symptoms of impending eclampsia appeared so that the administration had to be stopped. An identical amount of sodium given to 8 pregnant women with hypertension but no hypoproteinaemia caused small increments of weight but no other effects. Strauss considers that the manifestations of toxaemia result from water retention conditional on hypoproteinaemia, and finds that a high protein diet in such cases is beneficial, leading to diminution of oedema, provided salt is restricted. Perhaps the most convincing argument against

the view that hypoproteinaemia plays any important part in causing the oedema of toxaemia is that after delivery diuresis sets in and the oedema disappears rapidly at a time when the serum proteins are not materially increased. Eastman[176] states that in all his cases of oedema the serum proteins remained low for more than one week after delivery, whereas the oedema disappeared within a few days.

(b) *Increased Venous and Capillary Pressure.* While the colloid osmotic pressure of the plasma tends to draw water from the tissues into the blood, the hydrostatic pressure in the veins, and through them to the capillaries, tends to expel water from the blood into the tissues. An increase in the venous and capillary pressure might therefore cause oedema. Landis and Gibbon[149] showed that filtration of fluids out of capillaries is directly proportional to the venous pressure and therefore, as direct measurements of capillary pressure are difficult, measurements of venous pressure become important. Many such measurements have been made and on the whole show that in toxaemia there is no general increase. Burwell[150] found that in normal pregnancy the venous pressure was much higher in the leg than in the arm from the 4th month onwards. This was due chiefly to pressure by the enlarged uterus on the veins and evidently accounts for the tendency to oedema in the lower extremities in normal pregnancy. Thomson, Reid and Cohen[151] found the venous pressure in normal pregnancy within normal limits. In eclampsia and pre-eclamptic toxaemia it tended to be somewhat higher but was within the upper limits of normal. "Accompanying toxaemia of pregnancy there is apt to be a slight rise in venous pressure from the pre-toxaemic level but the rise is not an extreme one, and the level of venous pressure is in no way correlated to the severity of the illness, the amount of oedema, or the arterial blood-pressure."

(c) *Increased Capillary Permeability.* The capillaries are normally permeable only to water and dissolved salts, but not to proteins. If through any injury, whether by anoxia or by a chemical or other irritant, they become abnormally permeable, they will allow the passage of proteins in greater or less degree. The tissues containing the protein then acquire an osmotic pressure of their own and there will be a still greater tendency to the passage of water from the veins into the tissues with formation of oedema. Clearly, increased capillary permeability might well account for the often rapidly appearing oedema of toxaemia and it becomes, therefore, of the greatest importance to determine whether it is present or not. Strange to say there are very few studies of the protein content of the oedema fluid in toxaemia reported in the literature. The only relevant one is that by Hellmuth[152] who estimated the protein content of the oedema fluid obtained by puncture from 29 patients including 22 with pre-eclamptic toxaemia (pregnancy kidney) and 7 with eclampsia. He found the protein content to be low; in 26 it was less than 0.14 per cent and in 3 others it varied from 0.25 to 0.35 per cent. From this it may be assumed that capillary permeability is not increased even in the most severe cases. Petersen and Lash[153] reported that the protein content of oedema fluid was high, but as they determined it in blister fluid the result is obviously misleading, as application of a blister itself injures the capillaries underneath. Whether general capillary permeability is increased when albuminuria sets in is not known. The glomerular capillaries are then presumably more permeable, and if this is due to anoxia from arteriolar spasm it would probably be general throughout the body and might

then increase oedema already present. It is probable, however, that some at least of Hellmuth's patients had albuminuria and yet the protein content was low. This might be thought to cast doubt on the accuracy of Hellmuth's figures. The point to be noted here is that there is not any abnormal capillary permeability to account for the onset of oedema in the first place.

McLennan[154] studied the rate of filtration through the capillary walls in non-pregnant and normally pregnant women and in 12 patients with toxaemia, 9 of whom had albuminuria and 6 clinical oedema. He found that the average filtration rate in the toxaemic women was not significantly different from the non-pregnant controls.

(d) *Hormones Affecting Water Balance.* It has now been proved beyond any doubt that there is in the premenstrual phase of the menstrual cycle and in normal pregnancy an increased avidity of the tissues for sodium chloride and water expressing itself in delayed elimination and that this is due mainly if not entirely to the sex hormones. Harrop and Thorn[155] (1937) showed that subcutaneous injection of suprarenal cortical extract into normal dogs led to sodium retention. In view of the close structural similarity of these extracts to the female sex hormones Thorn and Harrop (1937) and Thorn and Engel[21] (1938) tested the effect of oestradiol and progesterone and found that they too caused diminished excretion of sodium and chloride and a reduced output of urine. The relation of these sex hormones to sodium retention in human pregnancy has been studied by Taylor, Warner and Welsh (1939,[22] 1943[156]) who have shown that in pregnancy and the puerperium sodium is retained during periods of high oestrogen and progesterone concentration and is lost after delivery or after death of the foetus when the concentration of these hormones is diminished. It was possible to prevent loss of sodium in the puerperium by injecting oestrogens. One might expect, therefore, to find an explanation of the still greater oedema of toxaemia in an increased serum and urine content of oestrogens and progestin. As we have already seen, all investigations, however, show that in toxaemia the oestrogen and progestin content are low (Smith and Smith, 1933[27] 1939[35]; Taylor and Scadron, 1940[31]). It is possible that the diminution in oestrogen is due to greater utilization, as Taylor suggests.

In view of the similar sodium retaining effect of cortical hormone (Harrop and Thorn[155]) and the clinical effect of the administration of corticosterone and desoxycorticosterone in causing massive oedema (see page 441), the possible *rôle* of the adrenal gland must be considered. In this connexion it may be recalled that Taylor, Warner and Welsh[22] found in 2 cases of toxaemia a pronounced divergence of the sodium and potassium lines on delivery, which " might indicate a return to normal from a previous condition of relatively low potassium and high sodium storage " that could theoretically have been produced by hyperactivity of the adrenal cortex. Against this view, however, they noted that in toxaemic cases they had found that potassium was also retained, whereas a lowered serum potassium and a high excretion rate are characteristic of suprarenal hyperactivity.*

It is apparent, therefore, that in the formation of oedema in pregnancy toxaemia many factors may be involved—a tendency to hypoproteinaemia, increased venous pressure from pressure of the uterus on the large veins (in the lower extremities only), increased capillary permeability (only after

* The reader is recommended to refer to the section headed " The Suprarenal Glands," p. 441, for a fuller account of the action of the adrenal cortical hormones.

albuminuria appears) and probably most important of all an increased concentration or utilization of the sex hormones. In all these instances the tendency to oedema is aggravated by a high intake of sodium and water. Strauss[51, 172, 173] de Snoo[178]. Whether the adrenal cortex plays any part has not been determined.

Hypertension.

Since 1934 our conception of the aetiology of hypertension in general has been dominated by the experimental work of Goldblatt and others,[165] who have shown that it is possible to produce persistent hypertension in animals by partially constricting one or both renal arteries so as to cause renal ischaemia. When the hypertension so produced is caused by constriction of one renal artery and the other kidney is normal it can be cured by removal of the ischaemic kidney. It has been shown that the hypertension is independent of nervous control for it occurs if all the nervous connexions of the kidney have been severed, and, indeed, if the kidney is transplanted into the neck. The mechanism is therefore a humoral one and it is now known that in the cortex of the ischaemic kidney there is produced a substance, renin, which is not in itself directly pressor but combines with an activator in the blood to produce angiotonin (hypertensin). Angiotonin has been isolated and it is found that if injected into human beings it reduces the effective renal blood flow, apparently by causing constriction of the efferent glomerular arterioles (Corcoran, Kohlstaedt and Page[136]), an effect, it will be noticed, the exact opposite of that caused by whatever pressor substance is at work in pre-eclamptic toxaemia.

It is evident, therefore, that the hypertension of eclamptic toxaemia cannot be due to a renin-hypertensin mechanism similar to that at work in the Goldblatt experiment, or to a primary renal ischaemia from any cause whatever, such as oedema of the kidney within its rigid capsule, or a thickening of the glomerular capillary basement membrane, or pressure of the enlarged uterus on the aorta or renal arteries as Goldblatt himself has suggested. Strauss assumed that a generalized oedema could of itself cause hypertension, presumably by means of cerebral oedema and anaemia, but we have already seen that in Rowntree dogs hypertension could not be caused by water intoxication unless posterior pituitary extract was administered at the same time, and that although the intracranial pressure was raised by the water intoxication alone.

Kellar and Sutherland[73] have shown in 35 women with toxaemia, by raising the temperature and thus abolishing vasoconstrictor nervous tone from the hand, that there was no increase in heat elimination such as might be due to vasodilatation. This proved that the pressor mechanism in toxaemia is humoral and not nervous. If this is accepted what is the origin of the pressor substance? We have seen that it is not angiotonin or tyramine. Adrenalin can also be excluded as it, like angiotonin and tyramine, causes constriction of the efferent glomerular arterioles and renal ischaemia (Goldring *et al.*[115]) Various other possibilities have been discussed previously in this review—posterior pituitary pressor substance, guanidine, and adrenal cortical hormones. And we have seen that there is experimental evidence (Byrom[18]) that the effect of pitressin can be augmented 10 times by oestrogens or gonadotrophic hormone.

It might be supposed that if a pressor substance were present in toxaemia it would be possible to find experimental evidence of it and several attempts have been made to do so. Solandt, Nassim and Cowan,[157] by cross two-way transfusion between

Goldblatt dogs and normal and nephrectomized dogs, showed that the blood of the hypertensive dogs contained a substance that produced transient hypertension in nephrectomized dogs, but not in dogs with normal intact kidneys. E. W. Page,[17] however, transfused 400 c.c. of blood from patients with eclampsia or severe pre-eclamptic toxaemia into normal pregnant women without producing any significant rise in blood-pressure.

It might be expected, too, that a circulating pressor substance in the pregnant toxaemic woman's blood would pass across the placenta into the blood of the foetus, so that the blood-pressure of the child of a toxaemic mother would be raised for a short period after its birth. Browne and Dodds[158] working on this hypothesis examined the blood-pressure of 6 normal infants 2 to 18 days old and of 3 toxaemics. The average systolic blood-pressure of the normal infants was 73 mm. Hg. In the 3 toxaemic infants, where the blood-pressure of the mother was 200/130, 220/100 and 200/140, the average systolic blood-pressure was 75 mm. There was thus no significant difference. Woodbury, Robinow and Hamilton[159] in 24 normal infants found the blood-pressure to be 80.1/46.3 and that of the infants of 8 toxaemic women 90.5/49.9. They conclude that "the babies born of toxaemic mothers probably have significantly higher systolic pressures." "These findings could be interpreted as favouring the view that there is a pressor substance in the blood of eclamptic patients which affects the infant's blood-pressure *via* the placental circulation."

Results of Injecting Pressor Substances in Normal and Pre-eclamptic Women. Experiments in which a pressor substance, tonephin, is injected intravenously into normal pregnant and non-pregnant women and patients with pre-eclamptic toxaemia (Shockaert and Lambillon,[160] de Valera and Kellar,[161] Browne[179]) have shown that while this produces a mild or moderate reaction and rise of systolic blood-pressure in the first two, in patients with pre-eclamptic toxaemia a much higher and longer lasting rise of blood-pressure was obtained. While the results of these 3 sets of workers differed in other details they all agreed on this, as will be seen from the following table.

Reactions to Pressor Substances (Rise of Systolic Arterial Pressure in mm. Hg.) in Normal and Toxaemic Women.
(Comparative results of various workers)

	Shockaert and Lambillon (Tonephin)	de Valera and Kellar (Tonephin)	Browne (Tonephin)
Normal women not pregnant	45	35	21.3
Normal pregnant women	13	23	33.2*
Pre-eclamptic toxaemia	55	43	54
Pregnancy with chronic hypertension	16	—	53
Normal puerperal	44	44	48.2

* All in the last 3 months of pregnancy.

The question now arises: how is the large increase of systolic blood-pressure in pre-eclamptic toxaemia in response to the injection of the pressor substance accounted for? Is the abnormal sensitivity to the pressor substance inborn and constitutional or has it been acquired by the woman in the course of her pregnancy? To answer this question the present writer (work unpublished) injected tonephin intravenously in 27 normal primiparae early in pregnancy—

usually about the 10th or 12th week. All the women, without exception, gave a mild reaction with an average rise of blood-pressure of 21/18 mm. Hg. from the ascertained base level. It was expected that 3 or 4 of the 27 would become toxaemic before the end of pregnancy, when the test should be repeated. At the time of writing only one has developed pre-eclamptic toxaemia. Tested with the same dose of tonephin as before she gave a reaction of 58/30 at the 37th week, her reaction at the 10th week of pregnancy having been only 22/18. This shows that the high reaction to pressor substances in pre-eclamptic toxaemia is not due to an inherited predisposition that makes these women unduly sensitive to pressor substances but to something that is acquired during their pregnancy, and seemingly after the 3rd month. It is possibly relevant to note here that Dill and Erickson,[162] in experiments on dogs and rabbits in which they applied clamps to the renal arteries in pregnant and non-pregnant animals, found that in the pregnant animals extremely severe and often fatal reactions occurred. Within 48 to 120 hours after the constriction was applied they developed weakness, lassitude, hypertension, albuminuria, haematuria, coma and convulsions. At postmortem examination they found renal lobular necrosis and coagulative necrosis and haemorrhages in the liver. In the non-pregnant animals no such rapidly fatal clinical course was seen, and Dill and Erickson[162] suggest that some factor other than simple renal insufficiency is concerned with the rapidly fatal course noted in the pregnant animals.

It thus appears that while we do not know the exact cause of the hypertension of pre-eclamptic toxaemia the possibilities have been considerably narrowed down, and we can say that (1) it is due to a humoral and not a nervous mechanism; (2) it is not due to renal ischaemia, however produced, nor to angiotonin (hypertensin) tyramine, or adrenalin; (3) during her pregnancy and probably after the 3rd month the woman who develops pre-eclamptic toxaemia acquires a certain sensitivity to the action of certain blood-pressure raising substances and this sensitivity does not seem to be due to any constitutional predisposition. Experimental work cited in the text (Byrom[18]) suggests that it may be due to oestrogenic or gonadotrophic hormone.

Albuminuria.

Albuminuria is almost always present in eclampsia though there are occasional exceptions (Theobald[42]). In pre-eclamptic toxaemia it never precedes hypertension and in the patient with essential hypertension who becomes pregnant it is always likely to appear if the systolic blood-pressure exceeds 160 mm. Hg. It therefore seems probable that it is due to vascular spasm affecting the afferent arterioles of the glomeruli, thus temporarily shutting off the blood supply to the glomerular capillaries. This view is supported by the work of Chesley, Markowitz and Wetchler,[134] who caused albuminuria in pregnant women by immersing the hand in ice water. Albuminuria invariably occurred if the blood-pressure rose more than 16 mm. Hg. both systolic and diastolic and it was concluded that its onset coincided with the release of the spasm. The spasm causes anoxia which if continued for more than 3 minutes damages the capillary wall and thus renders the glomeruli permeable to protein.

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ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

The Quarterly Meeting of the Council was held in the Medical Institution, Liverpool, on Saturday, 29th July, 1944, with the President, Mr. Eardley Holland, in the Chair.

Mr. Eardley Holland was re-elected President to take office in October next.

The following officers were also elected:—

Vice-Presidents:
Professor William Gough, Professor D. Dougal.

Honorary Treasurer:
Dr. J. P. Hedley.

Honorary Secretary:
Mr. G. F. Gibberd (R.A.M.C.)
Mr. W. Gilliatt was appointed Deputy Honorary Secretary in the absence of Mr. Gibberd on active service.

Honorary Librarian:
Mr. F. Roques (R.A.F.V.R.).

Honorary Curator of Museum:
Mr. A. W. Bourne.

The following candidate was admitted to the Membership *in absentia*:

Christina McDonald McTaggart.

The following were elected to Fellowship:

Dr. Leonard Colebrook, Dr. Leonard Gregory Parsons.

The following candidates were elected to Membership:

John Norman Inglis Emblin, John Paton Erskine, Alexander Havelock Maclennan, Agnes Muir Stewart, Elsie May Terry, Irene Marianne Titcomb.

INDEX TO CURRENT LITERATURE

In this Index an endeavour will be made, so far as war conditions permit, to maintain an up-to-date record of all titles bearing on obstetrics and gynaecology and the infant. The classification aims at making immediately available for the reader the titles under the various subject headings. In the majority of instances the title is obtained from the original publication. Where this has been impossible, the title has been obtained from the abstracting journal shown in brackets. Reprints will be welcomed and should be sent to the Editor.

Any inquiries should be addressed to Miss D. F. Atkins, British Postgraduate Medical School, Ducane Road, London, W. 12.

	REF.
ANATOMY	1
PHYSIOLOGY	6
PREGNANCY	
General	23
Normal	
Diagnosis	27
Duration	31
Nutrition	32
Abnormal	
Toxaemias	35
Association with disturbances of other maternal systems	40
Association with infectious diseases	56
Association with disturbances of the reproductive system	61
Placenta praevia	67
Abortion	68
Ectopic pregnancy	70
LABOUR	
Normal	72
Anaesthetics, analgesics	74
Abnormal	84
Dystocia, malpresentation	87
Multiple births	93
PUERPERIUM	
Normal	95
Lactation	96
Abnormal	100
Infections	101
THE INFANT	
General	104
Infections	117
Congenital defects	121
Blood	129
Nutrition	132

THE INFANT—*continued* REF.
Welfare ... 135
Mortality ... 139

MATERNAL WELFARE ... 142

MATERNAL MORTALITY ... 143

OBSTETRIC OPERATIONS ... 144

MISCELLANEOUS ... 149

GYNAECOLOGY
General ... 150
Disorders of function
Menstrual disorders ... 151
Menopause ... 157
Sterility ... 162
Abnormalities of the reproductive organs ... 167
Infections of the reproductive organs ... 169
New growths of the reproductive organs ... 174
Operations ... 200
Miscellaneous ... 202

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ANATOMY

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